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The document evaluates and assesses scientific information on the health and welfare effects associated with exposure to various concentrations of lead in ambient air. The literature through 1985 has been reviewed thoroughly for information relevant to air quality criteria, although the document is not intended as a complete and detailed review of all literature pertaining to lead. An attempt has been made to identify the major discrepancies in our current knowledge and understanding of the effects of these pollutants.

Although this document is principally concerned with the health and welfare effects of lead, other scientific data are presented and evaluated in order to provide a better understanding of this pollutant in the environment. To this end, the document includes chapters that discuss: the chemistry and physics of the pollutant; analytical levels; atmospheric chemistry and dispersion modeling; effects on vegetation; and respiratory, physiological, toxicological, clinical and epidemiological aspects of human exposure.

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Air Quality Criteria for Lead

Volume I of IV

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Air Quality Criteria for Lead

Volume I of IV

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Research and Development
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Environmental Criteria and Assessment Office
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LIST OF ABBREVIATIONS

AAS	Atomic absorption spectrometry
Ach	Acetylcholine
ACTH	Adrenocorticotrophic hormone
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADP/O ratio	Adenosine diphosphate/oxygen ratio
AIDS	Acquired immune deficiency syndrome
AIHA	American Industrial Hygiene Association
AII	Angiotensin II
ALA	Aminolevulinic acid
ALA-D	Aminolevulinic acid dehydrase
ALA-S	Aminolevulinic acid synthetase
ALA-U	Aminolevulinic acid in urine
APDC	Ammonium pyrrolidine-dithiocarbamate
APHA	American Public Health Association
ASTM	Amercian Society for Testing and Materials
ASV	Anodic stripping voltammetry
ATP	Adenosine triphosphate
B-cells	Bone marrow-derived lymphocytes
Ba	Barium
BAL	British anti-Lewisite (AKA dimercaprol)
BAP	benzo(a)pyrene
BSA	Bovine serum albumin
BUN	Blood serum urea nitrogen
BW	Body weight
C.V.	Coefficient of variation
CaBP	Calcium binding protein
CaEDTA	Calcium ethylenediaminetetraacetate
CaNa$_2$EDTA	Calcium sodium ethylenediaminetetraacetate
CBD	Central business district
Cd	Cadmium
CDC	Centers for Disease Control
CEC	Cation exchange capacity
CEH	Center for Environmental Health
CFR	reference method
CMP	Cytidine monophosphate
CNS	Central nervous system
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CP-U	Urinary coproporphyrin
C_{pah}	plasma clearance of p-aminohippuric acid
Cu	Copper
D.F.	Degrees of freedom
DA	Dopamine
δ-ALA	delta-aminolevulinic acid
DCMU	[3-(3,4-dichlorophenyl)-1,1-dimethylurea
DPP	Differential pulse polarography
DNA	Deoxyribonucleic acid
DTH	Delayed-type hypersensitivity
EEC	European Economic Community
EEG	Electroencephalogram
EMC	Encephalomyocarditis
EP	Erythrocyte protoporphyrin

LIST OF ABBREVIATIONS (continued).

EPA	U.S. Environmental Protection Agency
FA	Fulvic acid
FDA	Food and Drug Administration
Fe	Iron
FEP	Free erythrocyte protoporphyrin
FY	Fiscal year
G.M.	Grand mean
G-6-PD	Glucose-6-phosphate dehydrogenase
GABA	Gamma-aminobutyric acid
GALT	Gut-associated lymphoid tissue
GC	Gas chromatography
GFR	Glomerular filtration rate
HA	Humic acid
Hg	Mercury
hi-vol	High-volume air sampler
HPLC	High-performance liquid chromatography
i.m.	Intramuscular (method of injection)
i.p.	Intraperitoneally (method of injection)
i.v.	Intravenously (method of injection)
IAA	Indol-3-ylacetic acid
IARC	International Agency for Research on Cancer
ICD	International classification of diseases
ICP	Inductively coupled plasma emission spectroscopy
IDMS	Isotope dilution mass spectrometry
IF	Interferon
ILE	Isotopic Lead Experiment (Italy)
IRPC	International Radiological Protection Commission
K	Potassium
LDH-X	Lactate dehydrogenase isoenzyme x
LC_{50}	Lethyl concentration (50 percent)
LD_{50}	Lethal dose (50 percent)
LH	Luteinizing hormone
LIPO	Laboratory Improvement Program Office
ln	Natural logarithm
LPS	Lipopolysaccharide
LRT	Long range transport
mRNA	Messenger ribonucleic acid
ME	Mercaptoethanol
MEPP	Miniature end-plate potential
MES	Maximal electroshock seizure
MeV	Mega-electron volts
MLC	Mixed lymphocyte culture
MMD	Mass median diameter
MMED	Mass median equivalent diameter
Mn	Manganese
MND	Motor neuron disease
MSV	Moloney sarcoma virus
MTD	Maximum tolerated dose
n	Number of subjects or observations
N/A	Not Available

LIST OF ABBREVIATIONS (continued).

NA	Not Applicable
NAAQS	National ambient air quality standards
NAD	Nicotinamide Adenine Dinucleotide
NADB	National Aerometric Data Bank
NAMS	National Air Monitoring Station
NAS	National Academy of Sciences
NASN	National Air Surveillance Network
NBS	National Bureau of Standards
NE	Norepinephrine
NFAN	National Filter Analysis Network
NFR-82	Nutrition Foundation Report of 1982
NHANES II	National Health Assessment and Nutritional Evaluation Survey II
Ni	Nickel
NTA	Nitrilotriacetonitrile
OSHA	Occupational Safety and Health Administration
P	Phosphorus
p	Significance symbol
PAH	Para-aminohippuric acid
Pb	Lead
PBA	Air lead
$Pb(Ac)_2$	Lead acetate
PbB	concentration of lead in blood
PbBrCl	Lead (II) bromochloride
PBG	Porphobilinogen
PFC	Plaque-forming cells
pH	Measure of acidity
PHA	Phytohemagglutinin
PHZ	Polyacrylamide-hydrous-zirconia
PIXE	Proton-induced X-ray emissions
PMN	Polymorphonuclear leukocytes
PND	Post-natal day
PNS	Peripheral nervous system
P.O.	Per os (orally)
ppm	Parts per million
PRA	Plasma renin activity
PRS	Plasma renin substrate
PWM	Pokeweed mitogen
Py-5-N	Pyrimide-5'-nucleotidase
RBC	Red blood cell; erythrocyte
RBF	Renal blood flow
RCR	Respiratory control ratios/rates
redox	Oxidation-reduction potential
RES	Reticuloendothelial system
RLV	Rauscher leukemia virus
RNA	Ribonucleic acid
S-HT	Serotonin
SA-7	Simian adenovirus
S.C.	Subcutaneously (method of injection)
scm	Standard cubic meter
S.D.	Standard deviation
SDS	Sodium dodecyl sulfate
S.E.M.	Standard error of the mean

LIST OF ABBREVIATIONS (continued).

SES	Socioeconomic status
SGOT	Serum glutamic oxaloacetic transaminase
sIg	Surface immunoglobulin
SLAMS	State and local air monitoring stations
SMR	Standardized mortality ratio
Sr	Strontium
SRBC	Sheep red blood cells
SRMs	Standard reference materials
STEL	Short-term exposure limit
SW voltage	Slow-wave voltage
T-cells	Thymus-derived lymphocytes
t-tests	Tests of significance
TBL	Tri-n-butyl lead
TEA	Tetraethyl-ammonium
TEL	Tetraethyllead
TIBC	Total iron binding capacity
TML	Tetramethyllead
TMLC	Tetramethyllead chloride
TSH	Thyroid-stimulating hormone
TSP	Total suspended particulate
U.K.	United Kingdom
UMP	Uridine monophosphate
USPHS	U.S. Public Health Service
VA	Veterans Administration
V_d	Deposition velocity
VER	Visual evoked response
WHO	World Health Organization
XRF	X-Ray fluorescence
X^2	Chi squared
Zn	Zinc
ZPP	Erythrocyte zinc protoporphyrin

MEASUREMENT ABBREVIATIONS

dl	deciliter
ft	feet
g	gram
g/gal	gram/gallon
g/ha·mo	gram/hectare·month
km/hr	kilometer/hour
l/min	liter/minute
mg/km	milligram/kilometer
$\mu g/m^3$	microgram/cubic meter
mm	millimeter
μm	micrometer
μmol	micromole
ng/cm^2	nanograms/square centimeter
nm	nanometer
nM	nanomole
sec	second
t	tons

GLOSSARY VOLUME II

A horizon of soils - the top layer of soil, immediately below the litter layer; organically rich.

anorexia - loss of appetite.

anthropogenic - generated by the activities of man.

apoplast - extracellular portion of the root cross-section.

Brownian movement - the random movement of microscopic particles.

carnivore - meat-eating organism.

catenation - linkage between atoms of the same chemical element.

cation exchange capacity (CEC) - the ability of a matrix to selectively exchange positively charged ions.

chemical mass balance - the input/output balance of a chemical within a defined system.

coprophilic fungi - fungi which thrive on the biological waste products of other organisms.

detritus - the organic remains of plants and animals.

dictyosome - a portion of the chloroplast structurally similar to a stack of disks.

dry deposition - the transfer of atmospheric particles to surfaces by sedimentation or impaction.

ecosystem - one or more ecological communities linked by a common set of environmental parameters.

electronegativity - a measure of the tendency of an atom to become negatively charged.

enrichment factor - the degree to which the environmental concentration of an element exceeds the expected (natural or crustal) concentration.

galena - natural lead sulfide.

gravimetric - pertaining to a method of chemical analysis in which the concentration of an element in a sample is determined by weight (e.g., a precipitate).

herbivore - plant-eating organism.

humic substances - humic and fulvic acids in soil and surface water.

hydroponically grown plants - plants which are grown with their roots immersed in a nutrient-containing solution instead of soil.

Law of Tolerance - for every environmental factor there is both a minimum and a maximum that can be tolerated by a population of plants or animals.

leaf area index (LAI) - the effective leaf-surface (upfacing) area of a tree as a function of the plane projected area of the tree canopy.

LC_{50} - concentration of an agent at which 50 percent of the exposed population dies.

lithosphere - the portion of the earth's crust subject to interaction with the atmosphere and hydrosphere.

mass median aerodynamic diameter (MMAD) - the aerodynamic diameter (in μm) at which half the mass of particles in an aerosol is associated with values below and half above.

meristematic tissue - growth tissue in plants capable of differentiating into any of several cell types.

microcosm - a small, artificially controlled ecosystem.

mycorrhizal fungi - fungi symbiotic with the root tissue of plants.

NADP - National Atmospheric Deposition Program.

photolysis - decomposition of molecules into simpler units by the application of light.

photosystem I light reaction - the light reaction of photosystem converts light to chemical energy (ATP and reduced NADP). Photosystem I of the light reaction receives excited electrons from photosystem II, increases their energy by the absorption of light, and passes these excited electrons to redox substances that eventually produce reduced NADP.

primary producers - plants and other organisms capable of transforming carbon dioxide and light or chemical energy into organic compounds.

promotional energy - the energy required to move an atom from one valence state to another.

saprotrophs - heterotrophic organisms that feed primarily on dead organic material.

stoichiometry - calculation of the quantities of substances that enter into and are produced by chemical reactions.

stratospheric transfer - in the context of this document, transfer from the troposphere to the stratosphere.

symplast - intracellular portion of the root cross-section.

troposphere - the lowest portion of the atmosphere, bounded on the upper level by the stratosphere.

wet deposition - the transfer of atmospheric particles to surfaces by precipitation, e.g., rain or snow.

GLOSSARY VOLUME III

aerosol - a suspension of liquid or solid particles in a gas

BAL (British Anti-Lewisite) - a chelating agent often used in the treatment of metal toxicity

biliary clearance - an excretion route involving movement of an agent through bile into the GI tract

Brownian diffusion - the random movement of microscopic particles

"chelatable" or systemically active zinc - fraction of body's zinc store available or accessible to removal by a zinc-binding agent

chi-square goodness-of-fit tests - made to determine how well the observed data fit a specified model, these tests usually are approximately distributed as a chi-square variable

first-order kinetics - a kinetic process whose rate is proportional to the concentration of the species undergoing change

geochronometry - determination of the age of geological materials

hematocrit - the percentage of the volume of a blood sample occupied by cells

intraperitoneal - within the body cavity

likelihood function - a relative measure of the fit of observed data to a specified model. In some special cases it is equivalent to the sum of squares function used in least squares analysis.

mass median aerodynamic diameter (MMAD) - the aerodynamic diameter (in μm) at which half the mass of particles in an aerosol is associated with values below and half above

multiple regression analysis - the fitting of a single dependent variable to a linear combination of independent variables using least squares analysis is commonly called multiple regression analysis

plumburesis - lead excreted in urine

R^2 - this statistic, often called the multiple R squared, measures the proportion of total variation explained. A value near 1 means that nearly all of the variation is explained, whereas a value near zero means that almost none of the variation is explained.

GLOSSARY VOLUME IV

ADP/O ratio - a measure of the rate of respiration; the ratio of adenosine diphosphate concentration to oxygen levels increases as respiration is impaired

active transport - the translocation of a solute across a membrane by means of an energy-dependent carrier system capable of moving against a concentration gradient

affective function - pertaining to emotion

asthenospermia - loss or reduction of the motility of spermatozoa

azotemia - an excess of urea and other nitrogenous compounds in the blood

basal ganglia - all of the large masses of gray matter at the base of the cerebral hemispheres, including the corpus striatum, subthalamic nucleus, and substantia nigra

basophilic stippling - a histochemical appearance characteristic of immature erythrocytes

cognitive function - pertaining to reasoning, judging, conceiving, etc.

corpuscular volume - red blood cell volume

cristae - shelf-like infoldings of the inner membrane of mitochondria

cytomegaly - markedly enlarged cells

demyelination - destruction of the protective myelin sheath which surrounds most nerves

depolarization - the electrophysiological process underlying neural transmission

desaturation kinetic study - a form of kinetic study in which the rate of release of a species from its binding is studied

desquamation - shedding, peeling, or scaling off

disinhibition - removal of a tonic inhibitory effect

endoneurium - the delicate connective tissue enveloping individual nerve fibers within a nerve

erythrocyte - red blood cell

erythropoiesis - the formation of red blood cells

feedback derepression - the deactivation of a repressor

hepatocyte - a parenchymal liver cell

hyalinization - a histochemical marker characteristic of degeneration

hyperkalemia - a greater than normal concentration of potassium ions in the circulating blood

hyperplasia - increased numbers of cells

hypertrophy - increased size of cells

hypochromic - containing less than the normal amount of pigment

hyporeninemic hypoaldosteronism - pertaining to a systemic deficiency of renin and aldosterone

inclusion bodies - any foreign substance contained or entrapped within a cell

isocortex - cerebral cortex

lysosomes - a cytoplasmic, membrane-bound particle containing hydrolyzing enzymes

macrophage - large scavenger cell that ingests bacteria, foreign bodies, etc.

$(\text{Na}^+, \text{K}^+)$-ATPase - an energy-dependent enzyme which transports sodium and potassium across cell membranes

natriuresis - enhanced urinary excretion of sodium

normocytic - refers to normal, healthy-looking erythrocytes

organotypic - disease or cell mixture representative of a specific organ

oxidative phosphorylation - the generation of cellular energy in the presence of oxygen

paresis - partial or incomplete paralysis

pathognomic feature - characteristic or indicative of a disease

polymorphonuclear leukocytes - leukocytes (white blood cells) having nuclei of various forms

respiratory control rates (RCRs) - measure of intermediary metabolism

reticulocytosis - an increase in the number of circulating immature red blood cells

synaptogenesis - the formation of neural connections (synapses)

synaptosomes - morphological unit composed of nerve terminals and the attached synapse

teratogenic - affecting the development of an organism

teratospermia - a condition characterized by the presence of malformed spermatozoa

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The substance of this document and its addendum was reviewed by the Clean Air Scientific Advisory Committee of the Science Advisory Board in public sessions.

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1. EXECUTIVE SUMMARY AND CONCLUSIONS

1.1 INTRODUCTION

This criteria document evaluates and assesses scientific information on the health and welfare effects associated with exposure to various concentrations of lead in ambient air. According to Section 108 of the Clean Air Act of 1970, as amended in June, 1974, a criteria document for a specific pollutant or class of pollutants shall:

> . . . accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such pollutant in the ambient air, in varying quantities.

Air quality criteria are of necessity based on presently available scientific data, which in turn reflect the sophistication of the technology used in obtaining those data, as well as the magnitude of the experimental efforts expended. Thus, air quality criteria for atmospheric pollutants are a scientific expression of current knowledge and uncertainties. Specifically, air quality criteria are expressions of the scientific knowledge of the relationships between various concentrations--averaged over a suitable time period--of pollutants in the atmosphere and their adverse effects upon public health and the environment. Criteria are issued as a basis for making decisions about the need for control of a pollutant and as a basis for development of air quality standards governing the pollutant. Air quality criteria are descriptive; that is, they describe the effects that have been observed to occur as a result of external exposure at specific levels of a pollutant. In contrast, air quality standards are prescriptive; that is, they prescribe what a political jurisdiction has determined to be the maximum permissible exposure for a given time in a specified geographic area.

This criteria document is a revision of the previous Air Quality Criteria Document for Lead (EPA-600/8-77-017) published in December, 1977. This revision is mandated by the Clean Air Act (Sect. 108 and 109), as amended U.S.C. §§7408 and 7409. The criteria document sets forth what is known about the effects of lead contamination in the environment on human health and welfare. This requires that the relationship between levels of exposure to lead, via all routes and averaged over a suitable time period, and the biological responses to those levels be carefully assessed. Assessment of exposure must take into consideration the temporal and spatial distribution of lead and its various forms in the environment. Thus, the literature through December, 1985, has been reviewed thoroughly for information relevant to air quality criteria for lead; however, the document is not intended as a complete and detailed review of all literature pertaining to lead. Also, efforts are made to identify major discrepancies in our current knowledge and understanding of the effects of lead and its compounds.

1.2 ORGANIZATION OF DOCUMENT

This document focuses primarily on lead as found in its various forms in the ambient atmosphere; in order to assess its effects on human health, however, the distribution and biological availability of lead in other environmental media have been considered. The rationale for structuring the document was based primarily on the two major questions of exposure and response. The first portion of the document is devoted to lead in the environment--its physical and chemical properties; the monitoring of lead in various media; sources, emissions, and concentrations of lead; and the transport and transformation of lead within environmental media. The latter portion is devoted to biological responses and effects on human health and ecosystems.

In order to facilitate printing and distribution of the present materials, this Draft Final version of the revised EPA Air Quality Criteria Document for Lead is being released in four volumes. The first volume (Volume I) contains this executive summary and conclusions chapter (Chapter 1) for the entire document. Volume II contains Chapters 2-8, which include the following: the introduction for the document (Chapter 2); discussions of the above listed topics concerning lead in the environment (Chapters 3-7); and evaluation of lead effects on ecosystems (Chapter 8). The remaining two volumes contain Chapters 9-13, which deal with the extensive available literature relevant to assessment of health effects associated with lead exposure. In addition to the above materials, there is appended to Chapter 1 an addendum specifically addressing: the complex relationship between blood lead level and blood pressure; and the effects of fetal and pediatric exposures on growth and neurobehavioral development.

An effort has been made to limit the document to a highly critical assessment of the scientific data base through December, 1985. The references cited do not constitute an exhaustive bibliography of all available lead-related literature, but they are thought to be sufficient to reflect the current state of knowledge on those issues most relevant to the review of the ambient air quality standard for lead.

The status of control technology for lead is not discussed in this document. For information on the subject, the reader is referred to appropriate control technology documentation published by the Office of Air Quality Planning and Standards (OAQPS), U.S. EPA. The subject of "adequate margin of safety" stipulated in Section 108 of the Clean Air Act also is not explicitly addressed here; this topic will be considered in depth by EPA's Office of Air

Quality Planning and Standards in documentation prepared as a part of the process of revising the National Ambient Air Quality Standard (NAAQS) for Lead.

1.3 CHEMICAL AND PHYSICAL PROPERTIES OF LEAD

Lead is a gray-white metal of silvery luster that, because of its easy isolation and low melting point, was among the first of the metals to be extensively utilized by man. Lead was used as early as 2000 B.C. by the Phoenicians. The most abundant ore is galena, from which metallic lead is readily smelted. The metal is soft, malleable, and ductile, a poor electrical conductor, and highly impervious to corrosion. This unique combination of physical properties has led to its use in piping and roofing, and in containers for corrosive liquids. The metal and the dioxide are used in storage batteries, and organolead compounds are used in gasoline additives to boost octane levels. Since lead occurs in highly concentrated ores from which it is readily separated, the availability of lead is far greater than its natural abundance would suggest. The great environmental significance of lead is the result both of its utility and of its availability.

The properties of organolead compounds (i.e., compounds containing bonds between lead and carbon) are entirely different from those of the inorganic compounds of lead. Because of their use as antiknock agents in gasoline and other fuels, the most important organolead compounds have been the tetraalkyl compounds tetraethyllead (TEL) and tetramethyllead (TML). These lead compounds are removed from internal combustion engines by a process called lead scavenging, in which they react in the combustion chamber with halogenated hydrocarbon additives (notably ethylene dibromide and ethylene dichloride) to form lead halides, usually bromochlorolead(II).

The donor moiety in an organometallic complex could be almost any basic atom or molecule; the only requirement is that a donor, usually called a ligand, must have a pair of electrons available for bond formation. In general, the metal atom occupies a central position in the complex, as exemplified by the lead atom in tetramethyllead (Figure 1-1a) which is tetrahedrally surrounded by four methyl groups. In these simple organolead compounds, the lead is usually present as Pb(IV), and the complexes are relatively inert. These simple ligands, that bind to metal at only a single site, are called monodentate ligands. Some ligands, however, can bind to the metal atom by more than one donor atom, so as to form a heterocyclic ring structure. Rings of this general type are called chelate rings, and the donor molecules that form them are called polydentate ligands or chelating agents. In the chemistry of lead, chelation normally involves Pb(II). A wide variety of biologically significant chelates with ligands such as amino acids, peptides, and nucleotides are known. The simplest structure of this type occurs with the amino acid glycine, as represented in Figure 1-1b for a 1:2 (metal:ligand) complex. The importance of chelating agents in the present context is their widespread use in the treatment of lead and other metal poisoning.

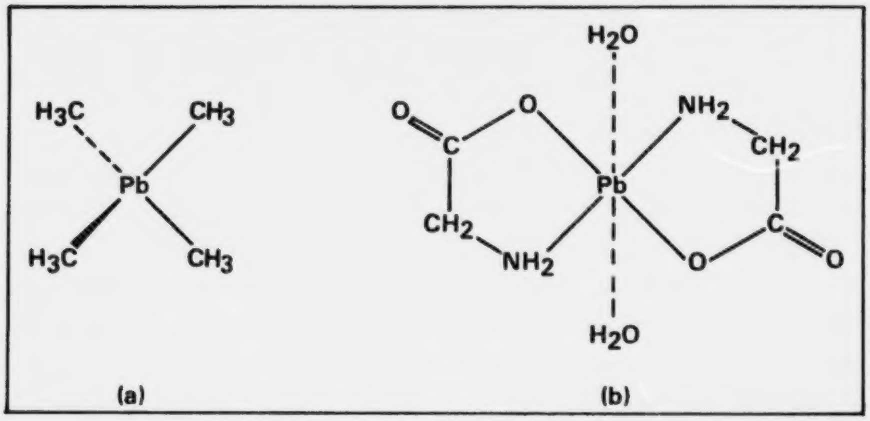

Figure 1-1. Metal complexes of lead.

Metals are often classified according to some combination of their electronegativity, ionic radius, and formal charge. These parameters are used to construct empirical classification schemes of relative hardness or softness. In these schemes, "hard" metals form strong bonds with "hard" anions and, likewise, "soft" metals bond with "soft" anions. Some metals are borderline, having both soft and hard character. Pb(II), although borderline, demonstrates primarily soft character (Figure 1-2). The term Class A may also be used to refer to hard metals, and Class B to soft metals. Since Pb(II) is a relatively soft (or class B) metal ion, it forms strong bonds to soft donor atoms like the sulfur atoms in the cysteine residues of proteins and enzymes. In living systems, lead atoms bind to these peptide residues in proteins, thereby changing the tertiary structure of the protein or blocking a substrate's approach to the active site of an enzyme. This prevents the proteins from carrying out their functions. As has been demonstrated in several studies (Jones and Vaughn, 1978; Williams and Turner, 1981; Williams et al., 1982), there is an inverse correlation between the LD_{50} values of metal complexes and the chemical softness parameter.

The role of the chelating agents is to compete with the peptides for the metal by forming stable chelate complexes that can be transported from the protein and eventually be excreted by the body. For simple thermodynamic reasons, chelate complexes are much more stable than monodentate metal complexes, and it is this enhanced stability that is the basis for their ability to compete favorably with proteins and other ligands for the metal ions.

It should be noted that both the stoichiometry and structures of metal chelates depend upon pH, and that structures different from those manifest in solution may occur in crystals. It will suffice to state, however, that several ligands can be found that are capable of sufficiently strong chelation with lead present in the body under physiological conditions to permit their use in the effective treatment of lead poisoning.

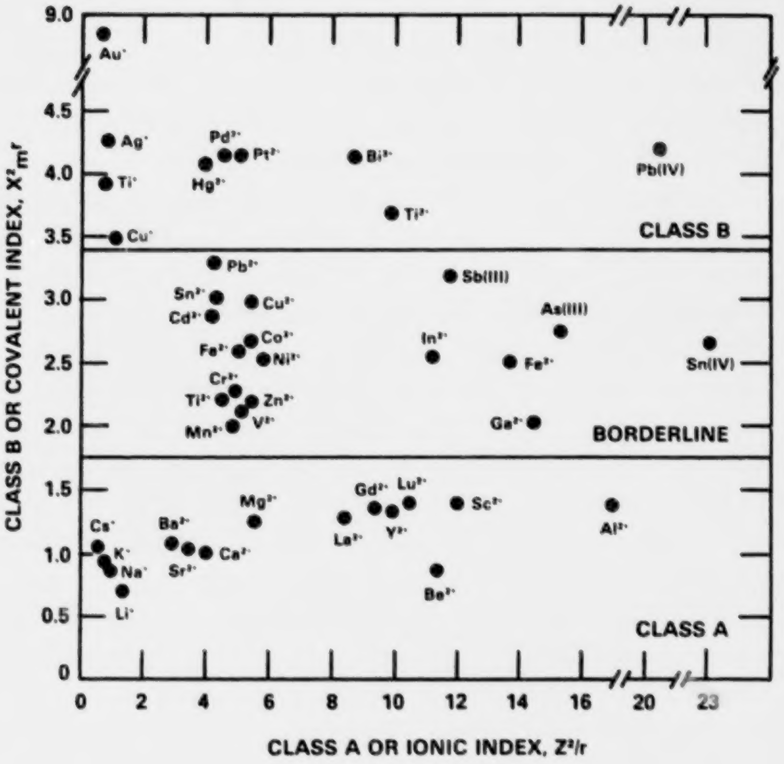

Figure 1-2. Softness parameters of metals.

Source: Nieboer and Richardson (1980).

1.4 SAMPLING AND ANALYTICAL METHODS FOR ENVIRONMENTAL LEAD

Lead, like all criteria pollutants, has a designated Reference Method for monitoring and analysis as required in State Implementation Plans for determining compliance with the lead National Ambient Air Quality Standard. The Reference Method uses a high volume sampler (hi-vol) for sample collection and atomic absorption spectrometry (AAS), inductively coupled plasma emission spectroscopy (ICP), or X-ray fluorescence (XRF) for analysis.

For a rigorous quality assurance program, it is essential that investigators recognize all sources of contamination and use every precaution to eliminate them. Contamination occurs on the surfaces of collection containers and devices, on the hands and clothing of the investigator, in the chemical reagents, in the laboratory atmosphere, and on the labware and tools used to prepare the sample for analysis.

1.4.1 Sampling Techniques

Sampling strategy encompasses site selection, choice of instrument used to obtain representative samples, and choice of method used to preserve sample integrity. In the United States, some sampling stations for air pollutants have been operated since the early 1950's. These early stations were a part of the National Air Surveillance Network (NASN), which has now become the National Filter Analysis Network (NFAN). Two other types of networks have been established to meet specific data requirements. State and Local Air Monitoring Stations (SLAMS) provide data from specific areas where pollutant concentrations and population densities are the greatest and where monitoring of compliance to standards is critical. The National Air Monitoring Station (NAMS) network is designed to serve national monitoring needs, including assessment of national ambient trends. SLAMS and NAMS stations are maintained by state and local agencies and the air samples are analyzed in their laboratories. Stations in the NFAN network are maintained by state and local agencies, but the samples are analyzed by laboratories in the U.S. Environmental Protection Agency, where quality control procedures are rigorously maintained.

Data from all three networks are combined into one data base, the National Aerometric Data Bank (NADB). These data may be individual chemical analyses of a 24-hour sampling period arithmetically averaged over a calendar period, or chemical composites of several filters used to determine a quarterly composite. Data are occasionally not available for a given location because they do not conform to strict statistical requirements.

In September, 1981, EPA promulgated regulations establishing ambient air monitoring and data reporting requirements for lead comparable to those already established in May of 1979 for the other criteria pollutants. Whereas sampling for lead is accomplished by sampling for total suspended particulate (TSP), the designs of lead and TSP monitoring stations must be complementary to insure compliance with the NAMS criteria for each pollutant. There must be at least two SLAMS sites for lead in any area that has a population greater than 500,000 and any area where lead concentration currently exceeds the ambient lead standard (1.5 $\mu g/m^3$) or has exceeded it since January 1, 1974.

To clarify the relationship between monitoring objectives and the actual siting of a monitor, the concept of a spatial scale of representativeness was developed. The spatial scales are described in terms of the physical dimensions of the air space surrounding the monitor throughout which pollutant concentrations are fairly similar. The time scale may also be an important factor. Siting criteria must include sampling times sufficiently long to include average windspeed and direction, or a sufficient number of samples must be collected over short sampling periods to provide an average value consistent with a 24-hour exposure.

Airborne lead is primarily inorganic particulate matter but may occur in the form of organic gases. Devices used for collecting samples of ambient atmospheric lead include the standard hi-vol sampler and a variety of other collectors employing filters, impactors, impingers, or scrubbers, either separately or in combination, that measure lead in μg/m^3. Some samplers measure lead deposition expressed in μg/cm^2; some instruments separate particles by size. As a general rule, particles smaller in mass median aerodynamic diameter (MMAD) than 2.5 μm are classified as "fine," and those larger than 2.5 μm as "coarse." The present SLAMS and NAMS employ the standard hi-vol sampler (U.S. Environmental Protection Agency, 1971) as part of their sampling networks. As a Federal Reference Method Sampler, the hi-vol operates with a specific flow rate of 1600-2500 m^3 of air per day.

When sampling ambient lead with systems employing filters, it is likely that vapor-phase organolead compounds will pass through the filter media. The use of bubblers downstream from the filter containing a suitable reagent or absorber for collection of these compounds has been shown to be effective. Organolead may be collected on iodine crystals, adsorbed on activated charcoal, or absorbed in an iodine monochloride solution.

Sampling of stationary sources for lead requires the use of a sequence of samplers in the smokestack. Since lead in stack emissions may be present in a variety of physical and chemical forms, source sampling trains must be designed to trap and retain both gaseous and particulate lead.

Three principal procedures have been used to measure mobile source emissions, specifically auto exhaust aerosols: a horizontal dilution tunnel, plastic sample collection bags, and a low residence time proportional sampler. In each procedure, samples are air-diluted to simulate roadside exposure conditions. The air dilution tube segregates fine combustion-derived particles from larger lead particles. Because the total exhaust plus dilution airflow is not held constant in this system, potential errors can be reduced by maintaining a very high dilution air/exhaust flow ratio. In the bag technique, auto emissions produced during simulated driving cycles are air-diluted and collected in a large plastic bag. This technique may result in errors of aerosol size analysis because of condensation of low vapor pressure organic substances onto the lead particles. To minimize condensation problems, a third technique, a low residence time proportional sampling system, has been used. This technique may be limited by the response time of the equipment to operating cycle phases that cause relatively small transients in the exhaust flow rate.

In sampling for airborne lead, air is drawn through filter materials such as glass fiber, cellulose acetate, or porous plastic. These materials often include contaminant lead that can interfere with the subsequent analysis. The type of filter and the analytical method to be used often determine the sample preparation technique. In some methods, e.g., X-ray fluorescence, analysis can be performed directly on the filter if the filter material is suitable.

The main advantages of glass fiber filters are low pressure drop and high particle collection efficiency at high flow rates. The main disadvantage is variability in the lead blank, which makes their use inadvisable in many cases. Teflon® filters have been used since 1975 by Dzubay et al. (1982) and Stevens et al. (1978), who have shown these filters to have very low lead blanks (<2 ng/cm^2). The collection efficiencies of filters, and also of impactors, have been shown to be dominant factors in the quality of the derived data.

Other primary environmental media that may be affected by airborne lead include precipitation, surface water, soil, vegetation, and foodstuffs. The sampling plans and the sampling methodologies used in dealing with these media depend on the purpose of the experiments, the types of measurements to be carried out, and the analytical technique to be used.

Lead concentration at the start of a rain event is higher than at the end, and rain striking the canopy of a forest may rinse dry deposition particles from the leaf surfaces. Rain collection systems should be designed to collect precipitation on an event basis and to collect sequential samples during the event. Two automated systems have recently been used. The Sangamo Precipitation Collector, Type A, collects rain in a single bucket exposed at the beginning of the rain event (Samant and Vaidya, 1982). A second sampler, described by Coscio et al. (1982), also remains covered between rain events; it can collect a sequence of eight samples during the period of rain and may be fitted with a refrigeration unit for sample cooling.

Because the physicochemical form of lead often influences environmental effects, there is a need to differentiate among the various chemical forms of lead in aqueous samples. Complete differentiation among all such forms is a complex task that has not yet been fully accomplished. The most commonly used approach is to distinguish between dissolved and suspended forms of lead. All lead passing through a 0.45 μm membrane filter is operationally defined as dissolved, while that retained on the filter is defined as suspended (Kopp and McKee, 1983). Containers used for sample collection and storage should be fabricated from essentially lead-free plastic or glass, e.g., conventional polyethylene, Teflon®, or quartz. These containers must be leached with hot acid for several days to ensure minimum lead contamination (Patterson and Settle, 1976).

The distance from emission sources and depth gradients must be considered in designing the sampling plan for lead in soil. Depth samples should be collected at not greater than 2 cm intervals to preserve vertical integrity. Because most soil lead is in chemical forms unavailable to plants, and because lead is not easily transported by plants, roots typically contain very little lead and shoots even less. Before analysis of plants, a decision must be made as to whether or not the plant leaf material should be washed to remove surface contamination from dry deposition and soil particles. If the plants are sampled for total lead content (e.g., if they serve as animal food sources), they cannot be washed; if the effect of lead on internal plant processes is being studied, the plant samples should be washed. In either case, the decision must be made at the time of sampling, as washing cannot be effective after the plant materials have dried.

1.4.2 Analytical Procedures

The choice of analytical method depends on the nature of the data required, the type of sample being analyzed, the skill of the analyst, and the equipment available. For general determination of elemental lead, atomic absorption spectroscopy (AAS) is widely used and recommended. Optical emission spectrometry and X-ray fluorescence (XRF) are rapid and inexpensive methods for multielemental analyses. X-ray fluorescence can measure lead concentrations reliably to 1 ng/m^3 using samples collected with commercial dichotomous samplers. Other analytical methods have specific advantages appropriate for special studies.

With respect to measuring lead without contamination during sample handling, several investigators have shown that the magnitude of the problem is quite large. It appears that the problem may be caused by failure to control the blank or by failure to standardize instrument operation (Patterson, 1983; Skogerboe, 1982). The laboratory atmosphere, collecting containers, and the labware used may be primary contributors to the lead blank problem (Patterson, 1983; Skogerboe, 1982). Failure to recognize these and other sources of contamination such as reagents and hand contact is very likely to result in the generation of artificially high analytical results. Samples with less than 100 ng lead should be analyzed in a clean laboratory especially designed for the elimination of lead contamination. Moody (1982) has described the construction and application of such a laboratory at the National Bureau of Standards.

For AAS, the lead atoms in the sample must be vaporized either in a precisely controlled flame or in a furnace. Furnace systems in AAS offer high sensitivity as well as the ability to analyze small samples. These enhanced capabilities are offset in part by greater difficulty in analytical calibration and by loss of analytical precision [lead analyses of 995 particulate samples from the NASN were accomplished by AAS with indicated precision of 11 percent (Scott et al., 1976)]. Disks (0.5 cm^2) are punched from air filters and analyzed by insertion of nichrome cups containing the disks into a flame. Another application involves the use of graphite cups as particle filters with the subsequent analysis of the cups directly in the furnace system. These two procedures offer the ability to determine particulate lead directly with minimal sample handling.

Techniques for AAS are still evolving. An alternative to the graphite furnace, evaluated by Jin and Taga (1982), uses a heated quartz tube through which the metal ion in gaseous hydride form flows continuously. Sensitivities were 1-3 ng/g for lead. The technique is similar to the hydride generators used for mercury, arsenic, and selenium. Other nonflame atomization systems, electrodeless discharge lamps, and other equipment refinements and technique developments have been reported (Horlick, 1982). More specialized AAS methods for the determination of tetraalkyl lead compounds in water and fish tissue have been described by Chau et al. (1979) and in air by Birnie and Noden (1980) and Rohbock et al. (1980).

Optical emission spectroscopy is based on the measurement of the light emitted by elements when they are excited in an appropriate energy medium. The technique has been used to determine the lead content of soils, rocks, and minerals at the 5-10 µg/g level with a relative standard deviation of 5-10 percent; this method has also been applied to the analysis of a large number of air samples. The primary advantage of this method is that it allows simultaneous measurement of a large number of elements in a small sample. In a study of environmental contamination by automotive lead, sampling times were shortened by using a sampling technique in which lead-free porous graphite was used both as the filter medium and as the electrode in the spectrometer.

More recent activities have focused attention on the inductively coupled plasma (ICP) system as a valuable means of excitation and analysis (Garbarino and Taylor, 1979). The ICP system offers a higher degree of sensitivity with less analytical interference than is typical of many of the other emission spectroscopic systems. Optical emission methods are inefficient when used for analysis of a single element, since the equipment is expensive and a high level of operator training is required. This problem is largely offset when analysis for several elements is required, as is often the case for atmospheric aerosols.

X-ray fluorescence (XRF) allows simultaneous identification of several elements, including lead, using a high-energy irradiation source. This technique offers the advantage that sample degradation can be kept to a minimum. On the other hand, X-ray emission induced by charged-particle excitation (proton-induced X-ray emission or PIXE) offers an attractive alternative to the more common techniques. The excellent capability of accelerator beams for X-ray emission analysis is partially due to the relatively low background radiation associated with the excitation; this is the basis of the electron microprobe method of analysis. When an intense electron beam is incident on a sample, it produces several forms of radiation, including X-rays, whose wavelengths depend on the elements present in the material and whose intensities depend on the relative quantities of these elements. The method is unique in providing compositional information on individual lead particles, thus permitting the study of dynamic chemical changes and perhaps allowing improved source identification.

Isotope dilution mass spectrometry (IDMS) is the most accurate measurement technique known at the present time. No other techniques serve more reliably as a comparative reference; it has been used for analyses of subnanogram concentrations of lead in a variety of sample types (Chow et al., 1969, 1974; Facchetti and Geiss, 1982; Hirao and Patterson, 1974; Murozumi et al., 1969; Patterson et al., 1976; Rabinowitz et al., 1973). The isotopic composition of lead peculiar to various ore bodies and crustal sources may also be used as a means of tracing the origin of anthropogenic lead.

Colorimetric or spectrophotometric analysis for lead using dithizone (diphenylthiocarbazone) as the reagent has been used for many years. It was the primary method recommended by a National Academy of Sciences (1972) report on lead, and the basis for the tentative method of testing for lead in the atmosphere by the American Society for Testing and Materials (1975b). Prior to the development of the IDMS method, colorimetric analysis served as the reference by which other methods were tested.

Analytical methods based on electrochemical phenomena are found in a variety of forms. They are characterized by a high degree of sensitivity, selectivity, and accuracy derived from the relationship between current, charge, potential, and time for electrolytic reactions in solutions. Anodic stripping voltammetry (ASV) is a two-step process in which the lead is preconcentrated onto a mercury electrode by an extended but selected period of reduction. After the reduction step, the potential is scanned either linearly or by differential pulse to oxidize the lead and allow measurement of the oxidation (stripping) current.

The majority of analytical methods are restricted to measurement of total lead and cannot directly identify the various compounds of lead. Gas chromatography (GC) using the electron capture detector has been demonstrated to be useful for organolead compounds. The use of atomic absorption as the GC detector for organolead compounds has been described by De Jonghe et al. (1981), while a plasma emission detector has been used by Estes et al. (1981). In addition, Messman and Rains (1981) have used liquid chromatography with an atomic absorption detector to measure organolead compounds. Mass spectrometry may also be used with gas chromatography (Mykytiuk et al., 1980).

1.5 SOURCES AND EMISSIONS

Lead is a naturally occurring element that may be found in the earth's crust and in all components of the biosphere. It may be found in water, soil, plants, animals, and humans. Because lead also occurs in ore bodies that have been mined for centuries by man, this metal has been distributed throughout the biosphere by the industrial activities of man. Of particular importance to the human environment are emissions of lead to the atmosphere. The sources of these emissions and the pathways of lead through the environment to man are shown in Figure 1-3. This figure shows natural inputs to soil by crustal weathering and anthropogenic inputs to the atmosphere from automobile emissions and stationary industrial sources. Natural emissions of lead to the atmosphere from volcanoes and windblown soil are of minor importance.

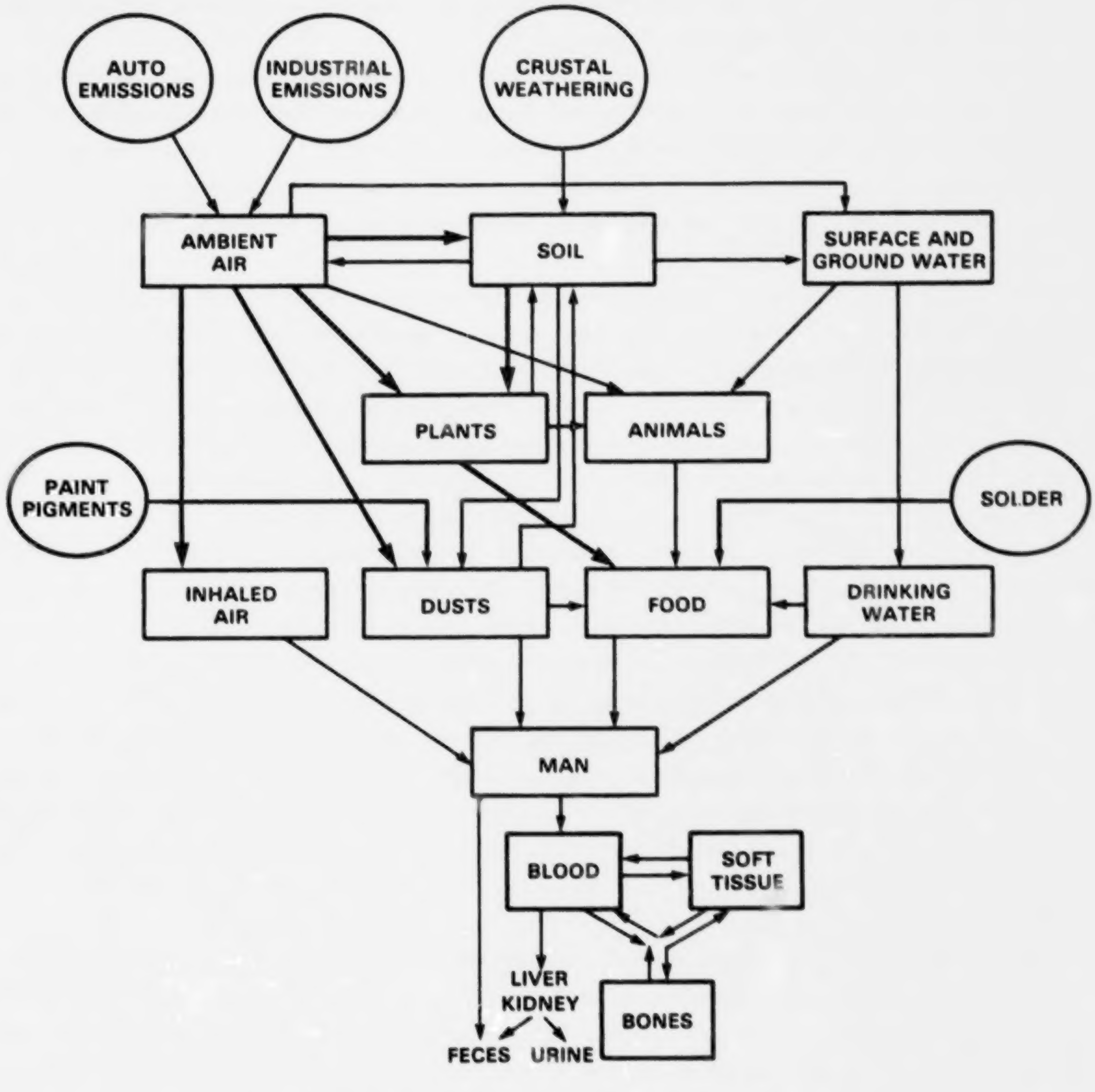

Figure 1-3. Pathways of lead from the environment to man, main compartments involved in partitioning of internal body burden of absorbed/retained lead, and main routes of lead excretion.

From these emission sources, lead moves through the atmosphere to various components of the human environment. Lead is deposited on soil and plants and in animals, becoming incorporated into the food chain of man. Atmospheric lead is a major component of household and street dust; lead is also inhaled directly from the atmosphere.

The history of global lead emissions has been assembled from chronological records of deposition in polar snow strata, marine and freshwater sediments, and the annual rings of trees. These records aid in establishing natural background levels of lead in air, soils, plants, animals, and humans, and they document the sudden increase in atmospheric lead at the time of the industrial revolution, with a later burst during the 1920's when lead-alkyls were first added to gasoline. Pond sediment analyses have shown a 20-fold increase in lead deposition during the last 150 years (Figure 1-4), documenting not only the increasing use of lead since the beginning of the industrial revolution in western United States, but also the relative fraction of natural versus anthropogenic lead inputs. Other studies have shown the same magnitude of increasing deposition in freshwater marine sediments. The pond and marine sediments also document the shift in isotopic composition of atmospheric lead caused by increased commercial use of the New Lead Belt in Missouri, where the ore body has an isotopic composition substantially different from other ore bodies of the world.

Perhaps the best chronological record is that of the polar ice strata of Murozumi et al. (1969), which extends nearly three thousand years back in time (Figure 1-4). At the South Pole, Boutron (1982) observed a 4-fold increase of lead in snow from 1957 to 1977 but saw no increase from 1927 to 1957. The author suggested the extensive atmospheric lead pollution that began in the 1920's did not reach the South Pole until the mid-1950's. This interpretation agrees with that of Maenhaut et al. (1979), who found atmospheric concentrations of lead of 0.000076 $\mu g/m^3$ at the same location. This concentration is about 3-fold higher than the 0.000024 $\mu g/m^3$ estimated by Patterson (1980) and Servant (1982) to be the natural lead concentration in the atmosphere. In summary, it is likely that atmospheric lead emissions have increased 2000-fold since the pre-Roman era, that even at this early time the atmosphere may have been contaminated by a factor of three over natural levels (Murozumi et al. 1969), and that global atmospheric concentrations have increased dramatically since the 1920's.

The history of global emissions may also be inferred from total production of lead. The historical picture of lead production has been pieced together from many sources by Settle and Patterson (1980) (Figure 1-5). Until the industrial revolution, lead production was determined largely by the ability or desire to mine lead for its silver content. Since that time, lead has been used as an industrial product in its own right, and efforts to improve smelter efficiency, including control of stack emissions and fugitive dusts, have made lead production more economical. This improved efficiency is not reflected in the chronological record because of atmospheric emissions of lead from many other anthropogenic sources, especially

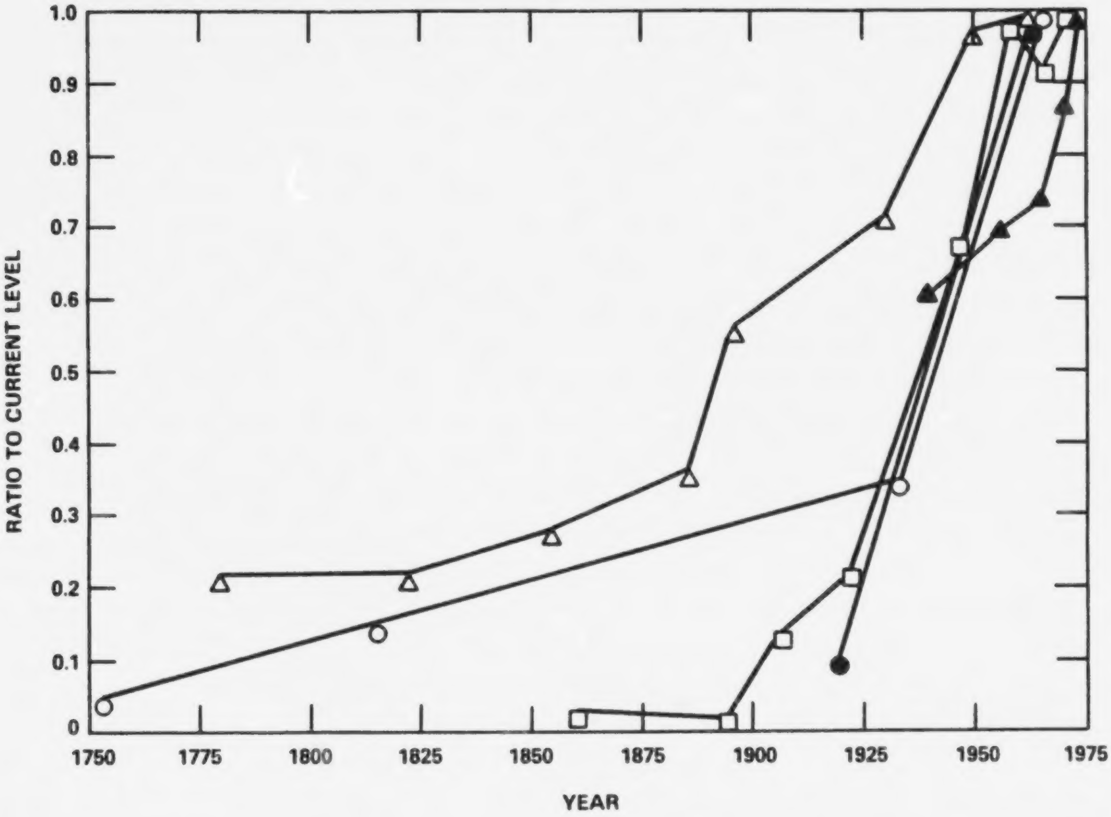

Figure 1-4. Chronological record of the relative increase of lead in snow strata, pond and lake sediments, marine sediments, and tree rings. The data are expressed as a ratio of the latest year of the record and should not be interpreted to extend back in time to natural or uncontaminated levels of lead concentration.

Source: Adapted from Murozumi et al. (1969) (○), Shirahata et al. (1980) (□), Edgington and Robbins (1976) (△), Ng and Patterson (1982) (▲), and Rolfe (1974) (●).

gasoline combustion. From this knowledge of the chronological record, it is possible to sort out contemporary anthropogenic emissions from natural sources of atmospheric lead.

Natural lead enters the biosphere from lead-bearing minerals in the lithosphere. In natural processes, lead is first incorporated in soil in the active root zone, from which it may be absorbed by plants, leached into surface waters, or eroded into windborne dusts. Calculations of natural contributions using geochemical information indicate that the natural particulate lead level is less than 0.0005 µg/m^3 (National Academy of Sciences, 1980), and probably lower than the 0.000076 µg/m^3 measured at the South Pole (Maenhaut et al., 1979). In contrast, lead concentrations in some urban environments may range as high as 6 µg/m^3 (U.S.

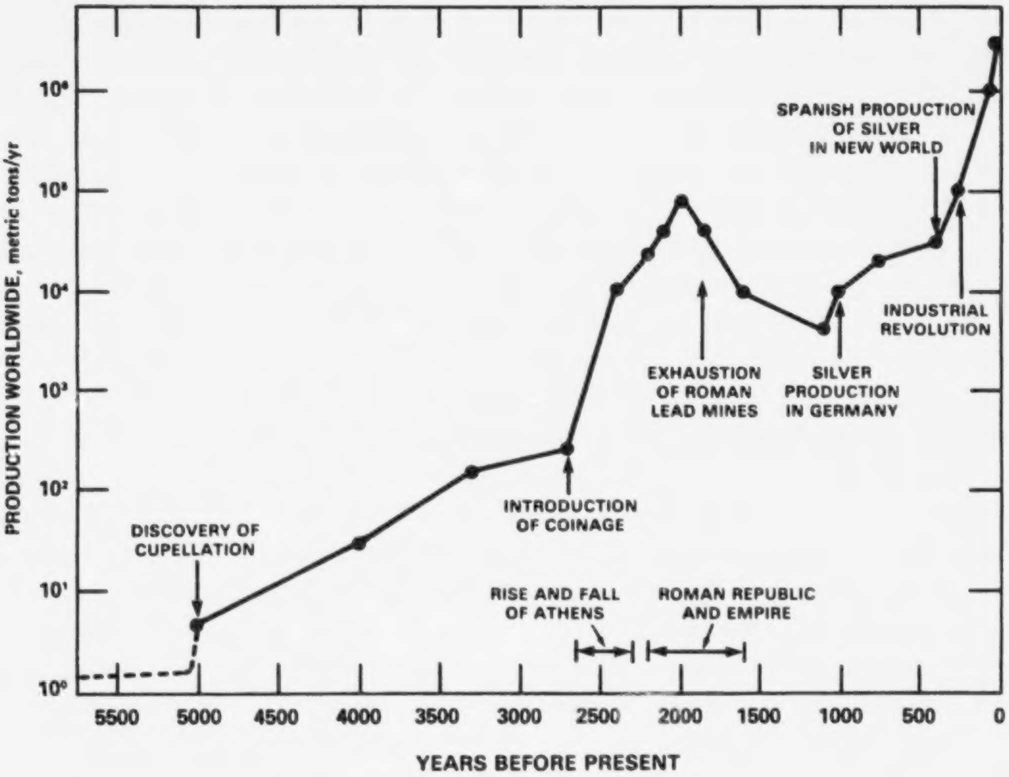

Figure 1-5. The global lead production has changed historically in response to major economic and political events. Increases in lead production (note log scale) correspond approximately to historical increases in lead emissions shown in Figure 5-1.

Source: Adapted from Settle and Patterson (1980).

Environmental Protection Agency, 1979, 1978). Evidently, most of this urban particulate lead originates from man-made sources.

Lead occupies an important position in the U.S. economy, ranking fifth among all metals in tonnage used. Approximately 85 percent of the primary lead produced in this country is from native mines, although often associated with minor amounts of zinc, cadmium, copper, bismuth, gold, silver, and other minerals (U.S. Bureau of Mines, 1972-1982). Missouri lead ore deposits account for approximately 80-90 percent of the domestic production. Total utilization averaged approximately 1.36×10^6 metric t/yr over the 10-year period, with storage batteries and gasoline additives accounting for approximately 70 percent of total use. Certain products, especially batteries, cables, plumbing, weights, and ballast, contain lead that is economically recoverable as secondary lead. Lead in pigments, gasoline additives, ammunition, foil, solder, and steel products is widely dispersed and therefore is largely unrecoverable. Approximately 40-50 percent of annual lead production is recovered and eventually recycled.

Lead or its compounds may enter the environment at any point during mining, smelting, processing, use, recycling, or disposal. Estimates of the dispersal of lead emissions into the environment by principal sources indicate that the atmosphere is the major initial recipient. Estimated lead emissions to the atmosphere are shown in Table 1-1. Mobile and stationary sources of lead emissions, although found throughout the nation, tend to be concentrated in areas of high population density, and near smelters. Figure 1-6 shows the approximate locations of major lead mines, primary and secondary smelters and refineries, and alkyl lead paints (International Lead Zinc Research Organization, 1982).

The majority of lead compounds found in the atmosphere result from leaded gasoline combustion. Several reports indicate that transportation sources contribute about 90 percent of the total atmospheric lead. Other mobile sources, including aviation use of leaded gasoline and diesel and jet fuel combustion, contribute insignificant lead emissions to the atmosphere.

Automotive lead emissions occur as PbBrCl in fresh exhaust particles. The fate of emitted lead particles depends upon particle size. Particles initially formed by condensation of lead compounds in the combustion gases are quite small (well under 0.1 μm in diameter). Particles in this size category are subject to growth by coagulation and, when airborne, can remain suspended in the atmosphere for 7-30 days and travel thousands of miles from their original source. Larger particles are formed as the result of agglomeration of smaller condensation particles and have limited atmospheric lifetimes.

During the lifetime of the vehicle, approximately 35 percent of the lead contained in the gasoline burned by the vehicle is emitted as small particles (<0.25 μm MMAD), and approximately 40 percent is emitted as larger particles (>10 μm MMAD) (Ter Haar et al., 1972). The remainder of the lead consumed in gasoline combustion is deposited in the engine and exhaust system.

Although the majority (>90 percent on a mass basis) of vehicular lead compounds are emitted as inorganic particles (e.g., PbBrCl), some organolead vapors (e.g., lead alkyls) are also emitted. The largest volume of organolead vapors arises from the manufacture, transport, and handling of leaded gasoline. Such vapors are photoreactive, and their presence in local atmospheres is transitory. Organolead vapors are most likely to occur in occupational settings and have been found to contribute less than 10 percent of the total lead present in the atmosphere.

TABLE 1-1. ESTIMATED ANTHROPOGENIC LEAD EMISSIONS TO THE ATMOSPHERE FOR THE UNITED STATES, 1984

Source Category	Annual (1984) emissions, (t/yr)	Percentage of total U.S. emissions
Gasoline combustion	34,881	89.4%
Waste oil combustion	781	2.0
Solid waste disposal	352	0.9
Coal combustion	265	0.7
Oil combustion	115	0.3
Gray iron production	54	0.1
Iron and steel production	427	1.1
Secondary lead smelting	278	0.7
Primary copper smelting	29	0.1
Ore crushing and grinding	116	0.3
Primary lead smelting	1150	2.8
Zn smelting	116	0.3
Other metallurgical	11	0.1
Lead alkyl manufacture	224	0.6
Lead acid battery manufacture	112	0.3
Portland cement production	70	0.2
Miscellaneous	35	0.1
Total	39,016[a]	100%

[a] Inventory does not include emissions from exhausting workroom air, burning of lead-painted surfaces, welding of lead-painted steel structures, or weathering of painted surfaces.

Source: Updated from Battye (1983).

The use of lead additives in gasoline, which increased in volume for many years, is now decreasing both because automobiles designed to use unleaded fuel constitute the major portion of the automotive population and because of two regulations promulgated by the U.S. Environmental Protection Agency (F.R., 1973 December 6). The first required the availability of unleaded fuel for use in automobiles designed to meet federal emission standards with lead-sensitive emission control devices (e.g., catalytic converters); the second required a reduction or phase-down of the lead content in leaded gasoline. The trend in lead content for U.S.

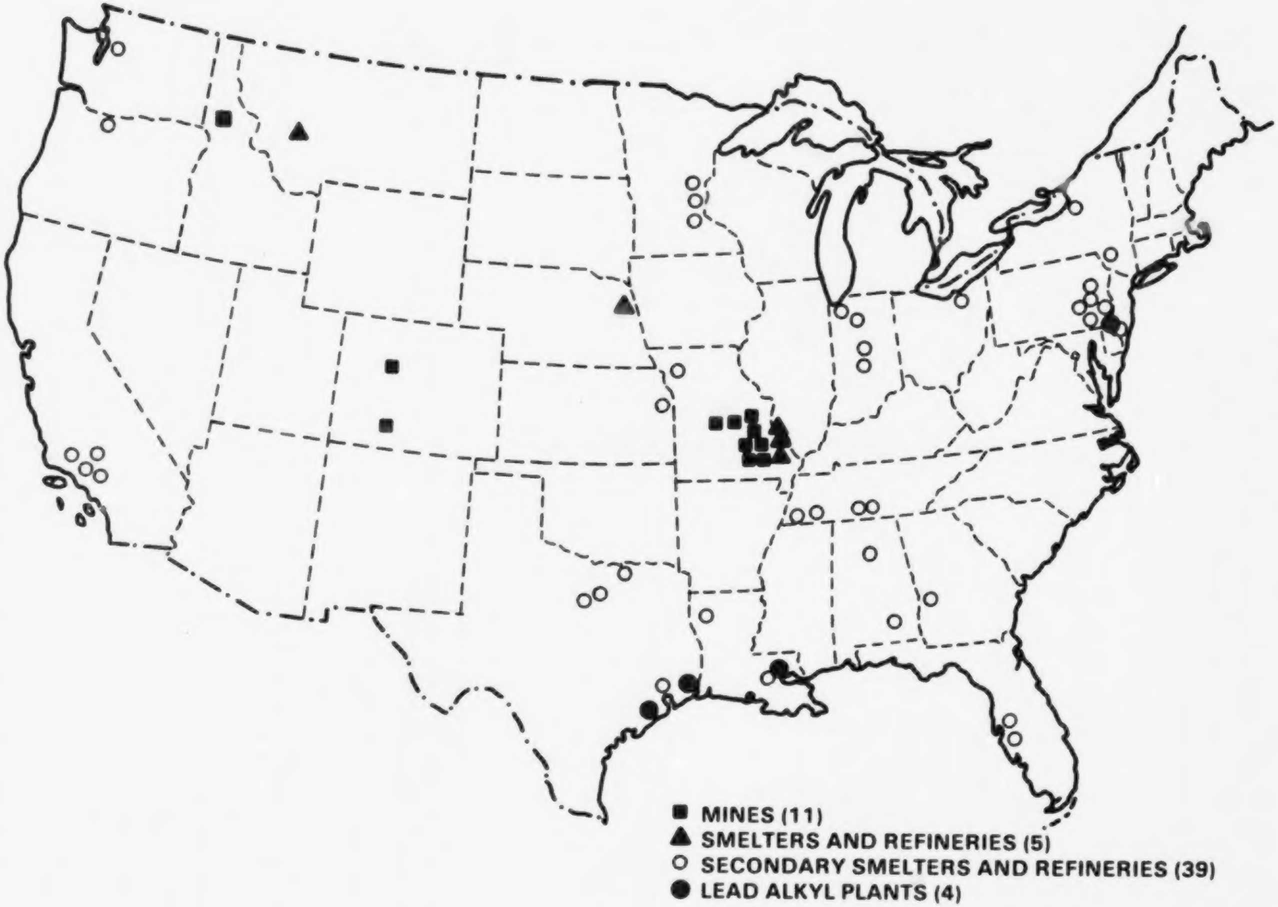
■ MINES (11)
▲ SMELTERS AND REFINERIES (5)
○ SECONDARY SMELTERS AND REFINERIES (39)
● LEAD ALKYL PLANTS (4)

Figure 1-6. Locations of major lead operations in the United States.

Source: International Lead Zinc Research Organization (1985).

gasolines is shown in Figure 1-7. Of the total gasoline pool, which includes both leaded and unleaded fuels, the average lead content decreased 73 percent, from an average of 1.62 g/gal in 1975 to 0.44 g/gal in 1984. The current allowable lead content of unleaded gasoline is 0.1 g/gal (F.R., 1985; March 7).

Data describing the lead consumed in gasoline and average ambient lead levels (composite of maximum quarterly values) versus calendar year are plotted in Figure 1-8. Between 1975 and 1984, the lead consumed in gasoline decreased 73 percent (from 167,400 to 46,000 metric tons) while the corresponding composite maximum quarterly average of ambient lead decreased 71 percent (from 1.23 to 0.36 $\mu g/m^3$). This indicates that control of lead in gasoline over the past several years has effected a direct decrease in peak ambient lead concentrations.

Solid waste incineration and combustion of waste oil are principal contributors of lead emissions from stationary sources. The manufacture of consumer products such as lead glass, storage batteries, and lead additives for gasoline also contributes significantly to stationary source lead emissions. Since 1970, the quantity of lead emitted from the metallurgical industry has decreased somewhat because of the application of control equipment and the closing of several plants, particularly in the zinc and pyrometallurgical industries.

A new locus for lead emissions emerged in the mid-1960s with the opening of the "Viburnum Trend" or "New Lead Belt" in southeastern Missouri. The presence of eight mines and three accompanying lead smelters in this area makes it the largest lead-producing district in the world.

1.6 TRANSPORT AND TRANSFORMATION

1.6.1 Atmospheric Transport

At any particular location and time, the concentration of lead found in the atmosphere depends on the proximity to the source, the amount of lead emitted from sources, and the degree of mixing provided by the motion of the atmosphere. Lead emissions at the tailpipe are typically around 24,000 $\mu g/m^3$, while lead values in city air are usually between 0.1 and 10 $\mu g/m^3$. These reduced concentrations are the result of dilution of effluent gas with clean air and the removal of particles by wet or dry deposition. Characteristically, lead concentrations are highest in confined areas close to sources and are progressively reduced by dilution or deposition in districts more removed from sources. In parking garages or tunnels, atmospheric lead concentrations can be ten to a thousand times greater than values measured near roadways or in urban areas. In turn, atmospheric lead concentrations are usually about 2½ times greater in the central city than in residential suburbs. Rural areas have even lower

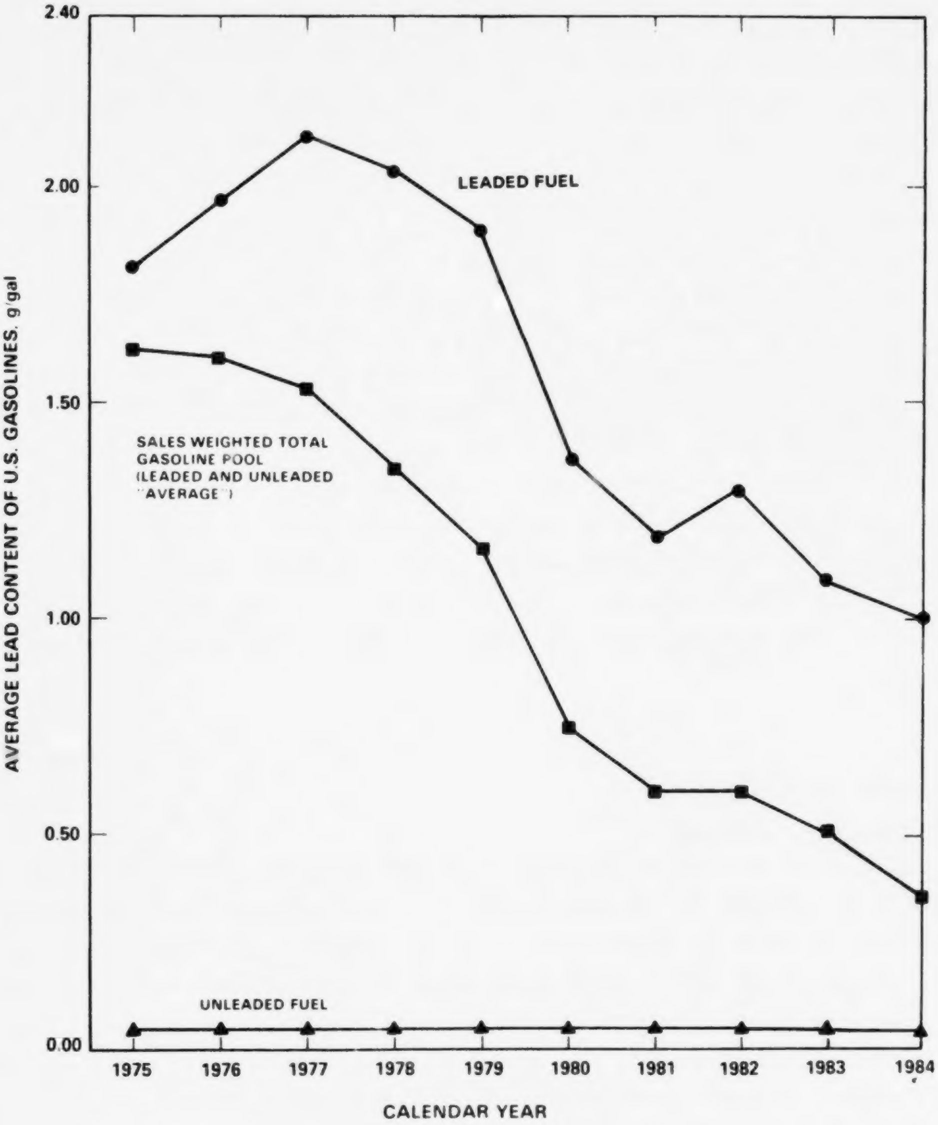

Figure 1-7. Trend in lead content of U.S. gasolines, 1975-1984.

Source: U.S. Environmental Protection Agency (1985).

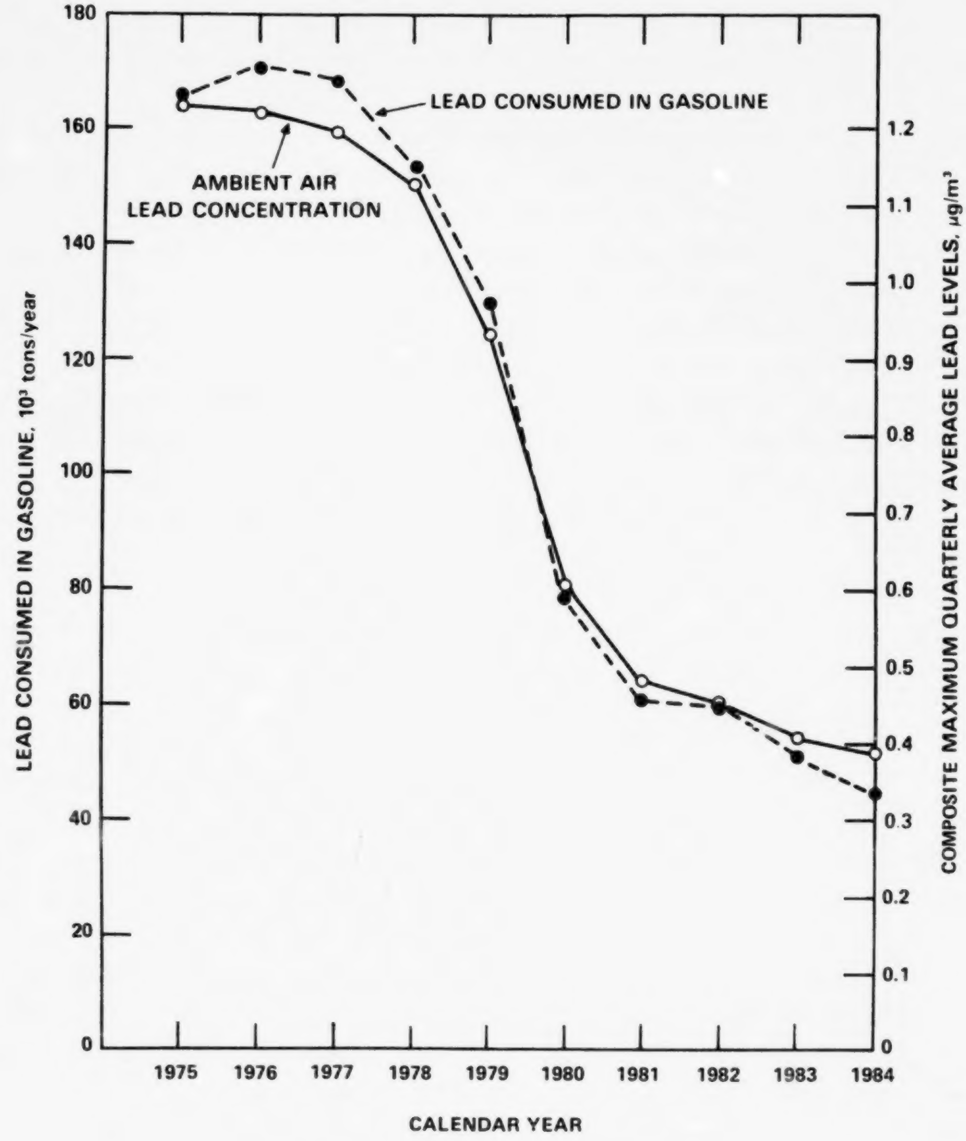

Figure 1-8. Lead consumed in gasoline and ambient lead concentrations, 1975-1984.

Source: U.S. Environmental Protection Agency (1985, 1986).

concentrations. Particle size distribution stabilizes within a few hundred kilometers of the sources, although atmospheric concentration continues to decrease with distance. Ambient organolead concentrations decrease more rapidly than inorganic lead, suggesting conversion from the organic to the inorganic phase during transport.

Whitby et al. (1975) placed atmospheric particles into three different size regimes: the nuclei mode (<0.1 µm); the accumulation mode (0.1-2 µm); and the large particle mode (>2 µm). At the source, lead particles are generally in the nuclei and large particle modes. Large particles are removed by deposition close to the source and particles in the nuclei mode diffuse to surfaces or agglomerate while airborne to form larger particles of the accumulation mode. Thus it is in the accumulation mode that particles are dispersed great distances.

Particles in air streams are subject to the same principles of fluid mechanics as particles in flowing water. The first principle is that of diffusion along a concentration gradient. If the airflow is steady and free of turbulence, the rate of mixing is determined by the diffusivity of the pollutant. By making generalizations of windspeed, stability, and surface roughness, it is possible to construct models using a variable transport factor called eddy diffusivity (K), in which K varies in each direction, including vertically. There is a family of K-theory models that describe the dispersion of particulate pollutants. The simplest K-theory model produces a Gaussian plume, called such because the concentration of the pollutant decreases according to a normal or Gaussian distribution in both the vertical and horizontal directions. These models have some utility and are the basis for most of the air quality simulations performed to date. Another family of models is based on the conservative volume element approach, where volumes of air are seen as discrete parcels having conservative meteorological properties. The effect of pollutants on these parcels of air, which may be considered to move along a trajectory that follows the advective wind direction, is expressed as a mixing ratio. None of the models have been tested for lead, and all require sampling periods of two hours or less in order for the sample to conform to a well-defined set of meteorological conditions; in most cases, such a sample would be below the detection limits for lead. The common pollutant used to test models is SO_2, which can be measured over very short, nearly instantaneous, time periods. The question of whether gaseous SO_2 can be used as a surrogate for particulate lead in these models remains to be answered.

Dispersion within confined situations, such as parking garages, residential garages, and tunnels, and away from expressways and other roadways not influenced by complex terrain features depends on emission rates and the volume of clean air available for mixing. These factors are relatively easy to estimate and some effort has been made to describe ambient lead concentrations that can result under selected conditions. On an urban scale, the routes of transport are not clearly defined, but can be inferred from an isopleth diagram, i.e., a plot connecting points of identical ambient concentrations. These plots always show that lead concentrations are maximum where traffic density is highest.

Dispersion beyond cities to regional and remote locations is complicated by the fact that there are no monitoring network data from which to construct isopleth diagrams, that removal by deposition plays a more important role with time and distance, and that emissions from many different geographic locations and sources converge. Dispersion from point sources such as smelters and refineries results in a concentration distribution pattern similar to urban dispersion, although the available data are notably less abundant. The 11 mines and 5 primary smelters and refineries shown in Figure 1-6 are not located in urban areas. Most of the 39 secondary smelters and refineries are likewise non-urban. Consequently, dispersion from these point sources should be considered separately, but in a manner similar to the treatment of urban regions. In addition to lead concentrations in air, concentrations in soil and on vegetation surfaces are often used to determine the extent of dispersion away from smelters and refineries.

Beyond the immediate vicinity of urban areas and smelter sites, lead in air declines rapidly to concentrations of 0.1-0.5 $\mu g/m^3$. Two mechanisms responsible for this change are dilution with clean air and removal by deposition. Some attempts have been made to reconcile air concentrations and deposition in remote locations with emission sources. Source reconciliation is based on the concept that each type of natural or anthropogenic emission has a unique combination of elemental concentrations. Measurements of ambient air, properly weighted during multivariate regression analysis, should reflect the relative amount of pollutant derived from each of several sources (Stolzenburg et al., 1982). Sievering et al. (1980) used the method of Stolzenburg et al. (1982) to analyze the transport of urban air from Chicago over Lake Michigan. They found that 95 percent of the lead in Lake Michigan air could be attributed to various anthropogenic sources, namely auto emissions, coal fly ash, cement manufacture, iron and steel manufacture, agricultural soil dust, construction soil dust, and incineration emissions. Cass and McRae (1983) used source reconciliation in the Los Angeles Basin to interpret 1976 NFAN data based on emission profiles from several sources. Their chemical element balance model showed that 20-22 percent of the total suspended particle mass could be attributed to highway sources.

Harrison and Williams (1982) determined air concentrations, particle size distributions, and total deposition flux at one urban and two rural sites in England. The urban site, which had no apparent industrial, commercial, or municipal emission sources, had an air lead concentration of 3.8 $\mu g/m^3$, whereas the two rural sites were about 0.15 $\mu g/m^3$. The average particle size became smaller toward the rural sites, as the MMAD shifted downward from 0.5 to 0.1 μm.

Purdue et al. (1973) measured both particulate and organic lead in atmospheric samples. They found that the vapor phase lead was about 5 percent of the total lead in most samples. It is noteworthy, however, that in an underground garage, total lead concentrations were approximately five times those in ambient urban atmospheres, and the organic lead increased to approximately 17 percent.

Knowledge of lead concentrations in the oceans and glaciers provides some insight into the degree of atmospheric mixing and long-range transport. Patterson and co-workers have measured dissolved lead concentrations in sea water off the coast of California, in the Central North Atlantic (near Bermuda), and in the Mediterranean. The profile obtained in the central northeast Pacific by Schaule and Patterson (1980) is shown in Figure 1-9. These investigators calculated that industrial lead currently is being added to the oceans at about 10 times the rate of introduction by natural weathering, with significant amounts being removed from the atmosphere by wet and dry deposition directly into the ocean. Their data suggest considerable contamination of surface waters near shore, diminishing toward the open ocean.

Ninety percent of the particulate pollutants in the global troposphere are injected in the northern hemisphere (Robinson and Robbins, 1971). Since the residence times for particles in the troposphere are much less than the interhemispheric mixing time, it is unlikely that significant amounts of particulate pollutants can migrate from the northern to the southern hemisphere via the troposphere. Murozumi et al. (1969) have shown that long-range transport of lead particles emitted from automobiles has significantly polluted the polar glaciers. They collected samples of snow and ice from Greenland (Figure 1-10) and the Antarctic. The authors attribute the gradient increase after 1750 to the Industrial Revolution and the accelerated increase after 1940 to the increased use of lead alkyls in gasoline. The most recent levels found in the Antarctic snows were, however, less than those found in Greenland by a factor of 10 or more.

Evidence from remote areas of the world suggests that lead and other fine particle components are transported substantial distances, up to thousands of kilometers, by general weather systems. The degree of surface contamination of remote areas with lead depends both on weather influences and on the degree of air contamination. However, even in remote areas, man's primitive activities can play an important role in atmospheric lead levels.

1.6.2 Deposition

Before atmospheric lead can have any effect on organisms or ecosystems, it must be transferred from the air to a surface. For natural ground surfaces and vegetation, this process may be either dry or wet deposition. Transfer by dry deposition requires that the particle

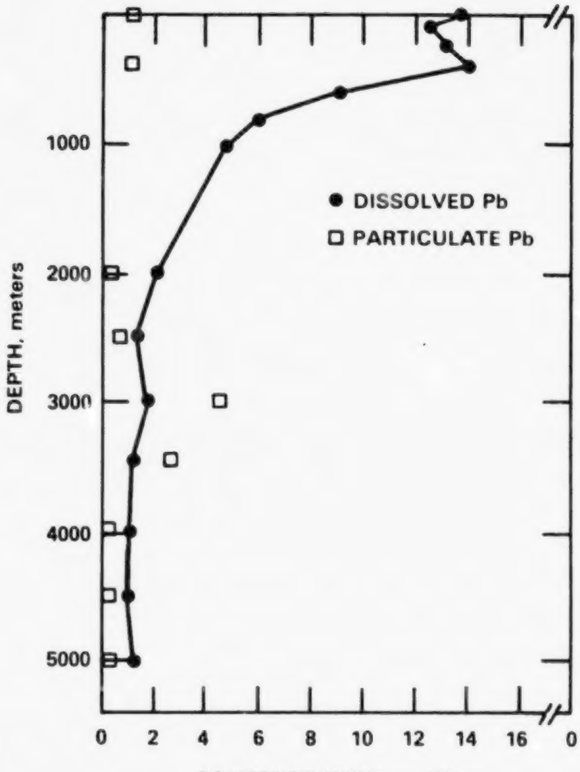

Figure 1-9. Profile of lead concentrations in the central northeast Pacific. Values below 1000 m are an order of magnitude lower than reported by Tatsumoto and Patterson (1963) and Chow and Patterson (1966).

Source: Schaule and Patterson (1980).

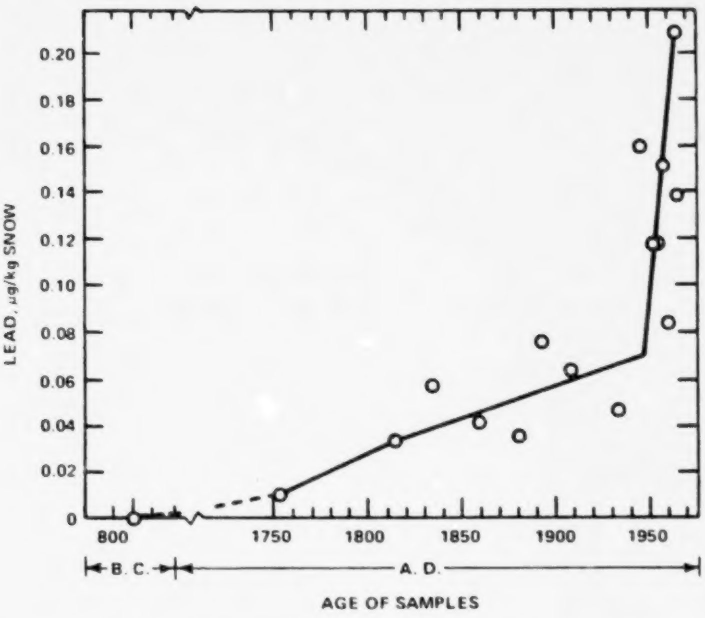

Figure 1-10. Lead concentration profile in snow strata of Northern Greenland.

Source: Murozumi et al. (1969).

move from the main airstream through the boundary layer to a surface. The boundary layer is defined as the region of minimal air flow immediately adjacent to that surface. The thickness of the boundary layer depends mostly on the windspeed and roughness of the surface. Airborne particles do not follow a smooth, straight path in the airstream. On the contrary, the path of a particle may be affected by micro-turbulent air currents, gravitation, or its own inertia. There are several mechanisms that may alter the particle path sufficient to cause transfer to a surface. These mechanisms are a function of particle size, windspeed, and surface characteristics.

Particles transported to a surface by any mechanism are said to have an effective deposition velocity (V_d) which is measured not by rate of particle movement but by accumulation on a surface as a function of air concentration. Several recent models of dry deposition have evolved from the theoretical discussion of Fuchs (1964) and the wind tunnel experiments of

Chamberlain (1966). The models of Slinn (1982) and Davidson et al. (1982) are particularly useful for lead deposition. Slinn's model considers a multitude of vegetation parameters to find several approximate solutions for particles in the size range of 0.1-1.0 µm MMAD, estimating deposition velocities of 0.01-0.1 cm/sec. The model of Davidson et al. (1982) is based on detailed vegetation measurements and wind data to predict a V_d of 0.05-1.0 cm/sec; deposition velocities are specific for each vegetation type. Both models show a decrease in deposition velocity as particle size decreases down to about 0.1-0.2 µm MMAD; as diameter decreases further from 0.1 to 0.001 µm MMAD, deposition velocity increases.

Several investigators have used surrogate surface devices to measure dry deposition rates. The few studies available on deposition of lead on vegetation surfaces show rates comparable to those of surrogate surfaces and deposition velocities in the range predicted by the models discussed above (Table 1-2). These data show that global emissions are in approximate balance with global deposition. The geochemical mass balance of lead in the atmosphere may be determined from quantitative estimates of inputs and outputs. Inputs amount to 450,000-475,000 metric tons annually. The amount of lead removed by wet deposition is approximately 208,000 metric t/yr (Table 1-3). The deposition flux for each vegetation type shown on Table 1-3 totals 202,000 metric t/yr. The combined wet and dry deposition is 410,000 metric tons, which compares favorably with the estimated 450,000 - 475,000 metric tons of emissions.

Concentrations of lead in ground water appear to decrease logarithmically with distance from a roadway. Rainwater runoff has been found to be an important transport mechanism in the removal of lead from a roadway surface in a number of studies. Apparently, only a light rainfall, 2-3 mm, is sufficient to remove 90 percent of the lead from the road surface to surrounding soil and to waterways. The lead concentrations in off-shore sediments often show a marked increase corresponding to anthropogenic activity in the region. Rippey et al. (1982) found such increases recorded in the sediments of Lough Neagh, Northern Ireland, beginning during the 1600's and increasing during the late 1800's. Data on recent lead levels indicate an average anthropogenic flux of 72 $mg/m^2 \cdot yr$, of which 27 $mg/m^2 \cdot yr$ could be attributed to direct atmospheric deposition. Prior to 1650, the total flux was 12 $mg/m^2 \cdot yr$, so there has been a 6-fold increase since that time. Ng and Patterson (1982) found prehistoric fluxes of 1-7 mg $Pb/m^2 \cdot yr$ to three offshore basins in southern California, which have now increased 3-to 9-fold to 11-21 $mg/m^2 \cdot yr$. Much of this lead is deposited directly from sewage outfalls, although at least 25 percent probably comes from the atmosphere.

TABLE 1-2. SUMMARY OF SURROGATE AND VEGETATION SURFACE DEPOSITION OF LEAD

Depositional surface	Flux, ng Pb/cm^2/day	Air conc, ng/m^3	Deposition velocity, cm/sec	Reference
Tree leaves (Paris)	0.38	---	0.086	1
Tree leaves (Tennessee)	0.29-1.2	---	---	2
Plastic disk (remote California)	0.02-0.08	13-31	0.05-0.4	3
Plastic plates (Tennessee)	0.29-1.5	110	0.05-0.06	4
Tree leaves (Tennessee)	---	110	0.005	4
Snow (Greenland)	0.004	0.1-0.2	0.1	5
Grass (Pennsylvania)	---	590	0.2-1.1	6
Coniferous forest (Sweden)	0.74	21	0.41	7

1. Servant, 1975
2. Lindberg et al., 1982
3. Elias and Davidson, 1980
4. Lindberg and Harriss, 1981
5. Davidson et al., 1981c, 1981b
6. Davidson et al., 1982
7. Lannefors et al., 1983

1.6.3 Transformation

Lead is emitted into the air from automobiles as lead halides and as double salts with ammonium halides (e.g., $PbBrCl \cdot 2NH_4Cl$). From mines and smelters, $PbSO_4$, $PbO \cdot PbSO_4$, and PbS appear to be the dominant species. In the atmosphere, lead is present mainly as the sulfate with minor amounts of halides. It is not completely clear just how the chemical composition changes in transport.

The ratio of Br to Pb is often cited as an indication of automotive emissions. From the mixtures commonly used in gasoline additives, the mass Br/Pb ratio should be 0.4-0.5. However, several authors have reported loss of halide, preferentially bromine, from lead salts in atmospheric transport; both photochemical decomposition and acidic gas displacement have been postulated as mechanisms. The Br/Pb ratios may be only crude estimates of automobile emissions; this ratio would decrease with distance from the highway from 0.39 to 0.35 at less proximate sites and 0.25 in suburban residential areas. For an aged aerosol, the Br/Pb mass

TABLE 1-3. ESTIMATED GLOBAL DEPOSITION OF ATMOSPHERIC LEAD

	Mass of water, 10^{17} kg/yr	Lead concentration, 10^{-6} g/kg	Lead deposition, 10^{6} kg/yr
Wet			
To oceans	4.1	0.4	164
To continents	1.1	0.4	44
Dry	Area 10^{12} m^2	Deposition rate 10^{-3} $g/m^2 \cdot yr$	Deposition 10^{6} kg/yr
To oceans, ice caps, deserts	405	0.2	89
Grassland, agricultural areas, and tundra	46	0.71	33
Forests	59	1.5	80
	Total dry:		202
	Total wet:		208
	Global:		410

Source: This report.

ratio is usually about 0.22. Habibi et al. (1970) studied the composition of auto exhaust particles as a function of particle size. Their main conclusions follow:

1. The chemical composition of emitted exhaust particles is related to particle size.
2. There is considerably more soot and carbonaceous material associated with fine-mode particles than with coarse-mode particles. Particulate matter emitted under typical driving conditions is rich in carbonaceous material.
3. Only small quantities of $2PbBrCl \cdot NH_4Cl$ were found in samples collected at the tailpipe from the hot exhaust gas. Lead-halogen molar ratios in particles of less than 10 μm MMAD indicate that much more halogen is associated with these solids than the amount expected from the presence of $2PbBrCl \cdot NH_4Cl$.

Lead sulfide is the main constituent of samples associated with ore handling and fugitive dust from open mounds of ore concentrate. The major constituents from sintering and blast furnace operations appeared to be $PbSO_4$ and $PbO \cdot PbSO_4$, respectively.

Atmospheric lead may enter the soil system by wet or dry deposition mechanisms. Lead could be immobilized by precipitation as less soluble compounds [$PbCO_3$, $Pb(PO_4)_2$], by ion exchange with hydrous oxides or clays, or by chelation with humic (HA) and fulvic (FA) acids. Lead immobilization is more strongly correlated with organic chelation than with iron and managanese oxide formation (Zimdahl and Skogerboe, 1977). The total capacity of soil to immobilize lead can be predicted from the linear relationship developed by Zimdahl and Skogerboe (1977) (Figure 1-11) based on the equation:

$$N = [2.8 \times 10^{-6} (A)] + [1.1 \times 10^{-5} (B)] - 4.9 \times 10^{-5}$$

where N is the saturation capacity of the soil expressed in moles/g soil, A is the cation exchange capacity of the soil in meq/100 g soil, and B is the pH.

The soil humus model also facilitates the calculation of lead in soil moisture using values available in the literature for conditional stability constants (K) with fulvic acid. The values reported for log K are linear in the pH range of 3-6 so that interpolations in the critical range of pH 4-5.5 are possible (Figure 1-11). Thus, at pH 4.5, the ratio of complexed lead to ionic lead is expected to be 3.8×10^3. For soils of 100 µg/g, the ionic lead in soil moisture solution would be 0.03 µg/g. It is also important to consider the stability constant of the Pb-FA complex relative to other metals. At normal soil pH levels of 4.5-8, lead is bound to FA + HA in preference to many other metals that are known plant nutrients (Zn, Mn, Ca, and Mg).

Soils have both a liquid and solid phase, and trace metals are normally distributed between these two phases. In the liquid phase, metals may exist as free ions or as soluble complexes with organic or inorganic ligands. Since lead rarely occurs as a free ion in the liquid phase, its mobility in the soil solution depends on the availability of organic or inorganic ligands. The liquid phase of soil often exists as a thin film of moisture in intimate contact with the solid phase. The availability of metals to plants depends on the equilibrium between the liquid and solid phase. In the solid phase, metals may be incorporated into crystalline minerals of parent rock material and secondary clay minerals or precipitated as insoluble organic or inorganic complexes. They may also be adsorbed onto the surfaces of any of these solid forms. Of these categories, the most mobile form is in soil moisture, where lead can move freely into plant roots or soil microorganisms with dissolved nutrients. The least mobile is parent rock material, where lead may be bound within crystalline structures over geologic periods of time; intermediate are the lead complexes and precipitates. Transformation from one form to another depends on the chemical environment of the soil. The water-soluble and exchangeable forms of metals are generally considered available for plant

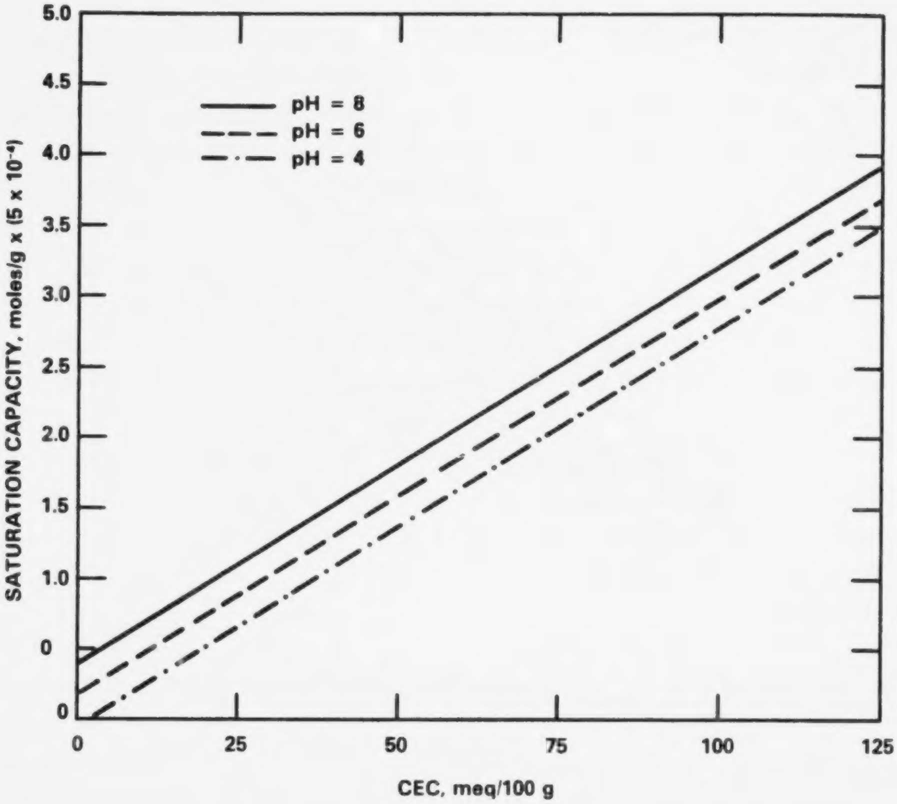

Figure 1-11. Variation of lead saturation capacity with cation exchange capacity in soil at selected pH values.

Source: Data from Zimdahl and Skogerboe (1977).

uptake. In normal soils, only a small fraction of the total lead is in exchangeable form (about 1 µg/g) and none exists as free lead ions. Of the exchangeable lead, 30 percent exists as stable complexes, 70 percent as labile complexes.

An outstanding characteristic of lead is its tendency to form compounds of low solubility with the major anions of natural water. The hydroxide, carbonate, sulfide, and more rarely the sulfate may act as solubility controls in precipitating lead from water. The amount of lead that can remain in solution is a function of the pH of the water and the dissolved salt content. A significant fraction of the lead carried by river water may be in an undissolved state. This insoluble lead can consist of colloidal particles in suspension or larger undissolved particles of lead carbonate, -oxide, -hydroxide, or other lead compounds incorporated in other components of particulate lead from runoff; it may occur either as sorbed ions or surface coatings on sediment mineral particles or be carried as a part of suspended living or nonliving organic matter.

The bulk of organic compounds in surface waters originates from natural sources. (Neubecker and Allen, 1983). The humic and fulvic acids that are primary complexing agents in soils are also found in surface waters at concentrations of 1-5 mg/l, occasionally exceeding 10 mg/l. The presence of fulvic acid in water has been shown to increase the rate of solution of lead sulfide 10-60 times over that of a water solution at the same pH that did not contain fulvic acid. At pH values near 7, lead-fulvic acid complexes are present in solution.

The transformation of inorganic lead, especially in sediment, to tetramethyllead (TML) has been observed and biomethylation has been postulated. However, Reisinger et al. (1981) have reported extensive studies of the methylation of lead in the presence of numerous bacterial species known to alkylate mercury and other heavy metals. In these experiments no biological methylation of lead was found under any condition. Chemical alkylation from methylcobalamine was found to occur in the presence of sulfide or of aluminum ion; chemical methylation was independent of the presence of bacteria.

1.7 ENVIRONMENTAL CONCENTRATIONS AND POTENTIAL PATHWAYS TO HUMAN EXPOSURE

In general, typical levels of human lead exposure may be attributed to four components of the human environment: inhaled air, dusts of various types, food, and drinking water. A baseline level of potential human exposure is determined for a normal adult eating a typical diet and living in a non-urban community. This baseline exposure is deemed to be unavoidable by any reasonable means. Beyond this level, additive exposure factors can be determined for other environments (urban, occupational, smelter communities), for certain habits and activities (smoking, drinking, pica, and hobbies), and for variations due to age, sex, or socioeconomic status.

1.7.1 Lead in Air

Ambient airborne lead concentrations may influence human exposure through direct inhalation of lead-containing particles and through ingestion of lead that has been deposited from the air onto surfaces. Our understanding of the pathways of human exposure is far from complete because most ambient measurements are not taken in conjunction with studies of the concentrations of lead in man or in components of his food chain.

The most complete set of data on ambient air concentrations may be extracted from the National Filter Analysis Network (NFAN) and its predecessors. In remote regions of the world, air concentrations are two or three orders of magnitude lower than in urban areas, lending credence to estimates of the concentrations of natural lead in the atmosphere. In the context of this data base, the conditions that modify ambient air (as measured by the monitoring networks) to air inhaled by humans cause changes in particle size distributions, changes with vertical distance above ground, and differences between indoor and outdoor concentrations.

The wide range of concentrations is apparent from Table 1-4, which summarizes data obtained from numerous independent measurements. Concentrations vary from 0.000076 $\mu g/m^3$ in remote areas to over 10 $\mu g/m^3$ near sources such as smelters. Many of the remote areas are far from human habitation and therefore do not reflect human exposure. However, a few of the regions characterized by small lead concentrations are populated by individuals with primitive lifestyles; these data provide baseline airborne lead data to which modern American lead exposures can be compared.

The remote area concentrations reported in Table 1-4 do not necessarily reflect natural, preindustrial lead. Murozumi et al. (1969) and Ng and Patterson (1981) have measured a 200-fold increase in the lead content of Greenland snow over the past 3000 years. The authors state that this lead originates in populated mid-latitude regions, and is transported over thousands of kilometers through the atmosphere to the Arctic. All of the concentrations in Table 1-4, including values for remote areas, have been influenced by anthropogenic lead emissions. It seems likely that the concentration of natural lead in the atmosphere is between 0.00002 and 0.00007 $\mu g/m^3$. A value of 0.00005 will be used for calculations regarding the contribution of natural air lead to total human uptake.

The effect of the 1978 National Ambient Air Quality Standard for Lead has been to reduce the air concentration of lead in major urban areas. Similar trends may also be seen in urban areas of smaller population density. There are many factors that can cause differences between the concentration of lead measured at a monitoring station and the actual inhalation of air by humans. Air lead concentrations usually decrease with vertical and horizontal distance from emission sources, and are generally lower indoors than outdoors.

Because people spend much of their time indoors, ambient air data may not accurately indicate actual exposure to airborne lead. Some studies show smaller indoor/outdoor ratios during the winter, when windows and doors are tightly closed. Overall, the data suggest indoor/outdoor ratios of 0.6-0.8 are typical for airborne lead in houses without air conditioning. Ratios in air-conditioned houses are expected to be in the range of 0.3-0.5 (Yocom, 1982). Even detailed knowledge of indoor and outdoor airborne lead concentrations at fixed locations may still be insufficient to assess human exposure to airborne lead. The study of Tosteson et al. (1982) included measurement of airborne lead concentrations using personal exposure monitors, carried by individuals going about their day-to-day activities. In contrast to the lead concentrations of 0.092 and 0.12 $\mu g/m^3$ at fixed locations, the average personal exposure was 0.16 $\mu g/m^3$. The authors suggest that the use of fixed monitors to assess exposure is inadequate at either indoor or outdoor locations.

TABLE 1-4. ATMOSPHERIC LEAD IN URBAN, RURAL, AND REMOTE AREAS OF THE WORLD

Location	Sampling period	Lead conc., ($\mu g/m^3$)	Reference
Urban			
New York	1978-79	1.1	NEDS, 1982
Boston	1978-79	0.8	NEDS, 1982
St. Louis	1973	1.1	NEDS, 1982
Houston	1978-79	0.9	NEDS, 1982
Chicago	1979	0.8	NEDS, 1982
Los Angeles	1978-79	1.4	NEDS, 1982
Ottowa	1975	1.3	NAPS, 1971-1976
Toronto	1975	1.3	NAPS, 1971-1976
Montreal	1975	2.0	NAPS, 1971-1976
Brussels	1978	0.5	Roels et al., 1980
Turin	1974-79	4.5	Facchetti and Geiss, 1982
Riyadh, Saudi Arabia	1983	5.5	El-Shobokshy, 1984
Rural			
New York Bight	1974	0.13	Duce et al., 1975
United Kingdom	1972	0.13	Cawse, 1974
Italy	1976-80	0.33	Facchetti and Geiss, 1982
Belgium	1978	0.37	Roels et al., 1980
Illinois	1973-74	0.23	Hudson et al., 1975
Remote			
White Mtn., CA	1969-70	0.008	Chow et al., 1972
High Sierra, CA	1976-77	0.021	Elias and Davidson, 1980
Olympic Nat. Park, WA	1980	0.0022	Davidson et al., 1982
Great Smoky Mtns. Nat. Park, TN	1979	0.015	Davidson et al., 1985
Glacier Nat. Park, MT	1981	0.0046	Davidson et al., 1985
South Pole	1974	0.000076	Maenhaut et al., 1979
Thule, Greenland	1965	0.0005	Murozumi et al., 1969
Thule, Greenland	1978-79	0.008	Heidam, 1983
Prins Christiansund, Greenland	1978-79	0.018	Heidam, 1983
Dye 3, Greenland	1979	0.00015	Davidson et al., 1981c
Eniwetok, Pacific Ocean	1979	0.00017	Settle and Patterson, 1982
Kumjung, Nepal	1979	0.00086	Davidson et al., 1981b
Bermuda	1973-75	0.0041	Duce et al., 1976
Abastumani Mtns. USSR	1979	0.019	Dzubay et al., 1984

1.7.2 Lead in Soil and Dust

Studies have determined that atmospheric lead is retained in the upper 2-5 cm of undisturbed soil, especially soils with at least 5 percent organic matter and a pH of 5 or above. There has been no general survey of this upper 2-5 cm of the soil surface in the United States, but several studies of lead in soil near roadsides and smelters and a few studies of lead in soil near old houses with lead-based paint can provide the backgound information for determining potential human exposures to lead from soil. Because lead is immobilized by the organic component of soil, the concentration of anthropogenic lead in the upper 2-5 cm is determined by the flux of atmospheric lead to the soil surface. Near roadsides, this flux is largely by dry deposition and the rate depends on particle size and concentration. In general, deposition flux drops off abruptly with increasing distance from the roadway. This effect is demonstrated in studies which show that surface soil lead decreases exponentially up to 25 m from the edge of the road. Roadside soils may contain concentrations of atmospheric lead ranging from 30 to 2000 µg/g in excess of natural levels within 25 meters of the roadbed, all in the upper layer of the soil profile.

Near primary and secondary smelters, lead in soil decreases exponentially within a 5-10 km zone around the smelter complex. Soil lead contamination varies with the smelter emission rate, length of time the smelter has been in operation, prevailing windspeed and direction, regional climatic conditions, and local topography.

Urban soils may be contaminated from a variety of atmospheric and non-atmospheric sources. The major sources of soil lead seem to be paint chips from older houses and deposition from nearby highways. Lead in soil adjacent to a house decreases with distance; this may be due to paint chips or to dust of atmospheric origin washing from the rooftop (Wheeler and Rolfe, 1979).

A definitive study that describes the source of soil lead was reported by Gulson et al. (1981) for soils in the vicinity of Adelaide, South Australia. In an urban to rural transect, stable lead isotopes were measured in the top 10 cm of soils over a 50 km distance. By their isotopic compositions, three sources of lead were identified: natural, non-automotive industrial lead from Australia, and tetraethyl lead manufactured in the United States. The results indicated most of the soil surface lead originated from leaded gasoline.

Lead may be found in inorganic primary minerals, on humic substances, complexed with Fe-Mn oxide films, on secondary minerals, or in soil moisture. All of the lead in primary minerals is natural and is bound tightly within the crystalline structure of the minerals. The lead on the surface of these minerals is leached slowly into the soil moisture. Atmospheric lead forms complexes with humic substances or on oxide films that are in equilibrium with soil moisture, although the equilibrium strongly favors the complexing agents.

Except near roadsides and smelters, only a few micrograms of atmospheric lead have been added to each gram of soil. Several studies indicate that this lead is available to plants and that even with small amounts of atmospheric lead, about 75 percent of the lead in soil moisture is of atmospheric origin.

Lead on the surfaces of vegetation may be of atmospheric origin. In internal tissues, lead may be of both atmospheric and soil origin. As with soils, lead on vegetation surfaces decreases exponentially with distance away from roadsides and smelters. This deposited lead is persistent. It is neither washed off by rain nor taken up through the leaf surface. Lead on the surface of leaves and bark is proportional to air lead concentrations and particle size distributions. Lead in internal plant tissues is directly, although not linearly, related to lead in soil.

1.7.3 Lead in Food

In a study to determine the background concentrations of lead and other metals in agricultural crops, the Food and Drug Administration (Wolnik et al., 1983), in cooperation with the U.S. Department of Agriculture and the U.S. Environmental Protection Agency, analyzed over 1500 samples of the most common crops taken from a cross section of geographic locations. Collection sites were remote from mobile or stationary sources of lead. Soil lead concentrations were within the normal range (8-25 µg/g) of U.S. soils. The concentrations of lead in crops are shown as "Total" concentrations on Table 1-5. The total concentration data should probably be seen as representing the lowest concentrations of lead in food available to Americans. The data on these ten crops suggest that root vegetables have lead concentrations between 0.0046 and 0.009 µg/g, all of which is soil lead. Aboveground parts not exposed to significant amounts of atmospheric deposition (sweet corn and tomatoes) have less lead internally. If it is assumed that this same concentration is the internal concentration for aboveground parts for other plants, it is apparent that five crops have direct atmospheric deposition in proportion to surface area and estimated duration of exposure. The deposition rate of 0.04 $ng/cm^2 \cdot day$ in rural environments could account for these amounts of direct atmospheric lead. Lead in food crops varies according to exposure to the atmosphere and in proportion to the effort taken to separate husks, chaff, and hulls from edible parts during processing for human or animal consumption. Root parts and protected aboveground parts contain natural lead and indirect atmospheric lead, both of which are derived from the soil. For exposed aboveground parts, any lead in excess of the average of unexposed aboveground parts is considered to have been directly deposited from the atmosphere.

TABLE 1-5. BACKGROUND LEAD IN BASIC FOOD CROPS AND MEATS
(μg/g fresh weight)

Crop	Natural Pb	Indirect atmospheric	Direct atmospheric	Total†
Wheat	0.0015	0.0015	0.034	0.037
Potatoes	0.0045	0.0045	--	0.009
Field corn	0.0015	0.0015	0.019	0.022
Sweet corn	0.0015	0.0015	--	0.003
Soybeans	0.021	0.021	--	0.042
Peanuts	0.005	0.005	--	0.010
Onions	0.0023	0.0023	--	0.0046
Rice	0.0015	0.0015	0.004	0.007
Carrots	0.0045	0.0045	--	0.009
Tomatoes	0.001	0.001	--	0.002
Spinach	0.0015	0.0015	0.042	0.045
Lettuce	0.0015	0.0015	0.010	0.013
Beef (muscle)	0.0002	0.002	0.02	0.02*
Pork (muscle)	0.0002	0.002	0.06	0.06*

†Except as indicated, data are from Wolnik et al. (1983, 1985).

*Data from Penumarthy et al. (1980).

1.7.4 Lead in Water

Lead occurs in untreated water in either dissolved or particulate form. Because atmospheric lead in rain or snow is retained by soil, there is little correlation between lead in precipitation and lead in streams that drain terrestrial watersheds. Rather, the important factors seem to be the chemistry of the stream (pH and hardness) and the volume of the stream flow. The concentration of lead in streams and lakes is also influenced by the lead content of sediments. At neutral pH, lead moves from the dissolved to particulate form; the particles eventually pass to sediments. At low pH, the reverse pathway is generally the case. Hardness, which is a combination of the Ca and Mg concentration, can also influence the solubility of lead; at higher concentrations of Ca and Mg, its solubility decreases.

For groundwater, chemistry is also important, as is the geochemical composition of the water-bearing bedrock. Municipal and private wells typically have a neutral pH and somewhat higher-than-average hardness. Lead concentrations are not influenced by acid rain, surface runoff, or atmospheric deposition. Rather, the primary determinant of lead concentration is the geochemical makeup of the bedrock that is the source of the water supply. Groundwater typically ranges from 1 to 100 μg Pb/l (National Academy of Sciences, 1980).

Whether from surface or ground water supplies, municipal waters undergo extensive chemical treatment prior to release to the distribution system. Although there is no direct effort to remove lead from the water supply, some treatments, such as flocculation and sedimentation, may inadvertently remove lead along with other undesirable substances. On the other hand, chemical treatment to soften water increases the solubility of lead and enhances the possibility that lead will be added to water as it passes through the distribution system. For samples taken at the household tap, lead concentrations are usually higher in the initial volume (first daily flush) than after the tap has been running for some time. Water standing in the pipes for several hours is intermediate between these two concentrations. (Sharrett et al., 1982; Worth et al., 1981).

1.7.5 Baseline Exposures to Lead

Lead concentrations in environmental media that are in the pathway of human consumption are summarized on Table 1-6. Because natural lead is generally three to four orders of magnitude lower than anthropogenic lead in ambient rural or urban air, all atmospheric contributions of lead are considered to be of anthropogenic origin. Natural soil lead typically ranges from 10 to 30 μg/g, but much of this is tightly bound within the crystalline matrix of soil minerals at normal soil pHs of 4-8. Lead in the organic fraction of soil is part natural and part atmospheric. The fraction derived from fertilizer is considered to be minimal. In undisturbed rural and remote soils, the ratio of natural to atmospheric lead is about 1:1, perhaps as high as 1:3. This ratio persists through soil moisture and into internal plant tissues.

TABLE 1-6. SUMMARY OF ENVIRONMENTAL CONCENTRATIONS OF LEAD

Medium	Natural lead	Atmospheric lead	Total lead
Air (urban) ($\mu g/m^3$)	0.00005	0.3 - 1.1	0.3 - 1.1
Air (rural) ($\mu g/m^3$)	0.00005	0.15 - 0.3	0.15 - 0.3
Soil total (μg/g)	8-25	3 - 5	10 - 30
Food crops (μg/g)	0.0025	0.002 - 0.045	0.002 - 0.045
Surface water (μg/g)	0.00002	0.005 - 0.030	0.005 - 0.030
Ground water (μg/g)	0.003	--	0.001 - 0.1

In tracking air lead through pathways of human exposure, it is necessary to distinguish between atmospheric lead that has passed through the soil, called indirect atmospheric here, and atmospheric lead that has deposited directly on crops or water. Because indirect atmospheric lead will remain in the soil for many decades, this source is insensitive to projected changes in atmospheric lead concentrations.

Initially, a current baseline exposure scenario is described for an individual with a minimum amount of daily lead consumption. This person would live and work in a nonurban environment, eat a normal diet of food taken from a typical grocery shelf, and would have no habits or activities that would tend to increase lead exposure. Lead exposure at the baseline level is considered unavoidable without further reductions of lead in the atmosphere or in canned foods. Most of the baseline lead is of anthropogenic origin.

To arrive at a minimum or baseline exposure for humans, it is necessary to begin with the environmental components (air, soil, food crops, and water) that are the major sources of lead consumed by humans (Table 1-6). These components are measured frequently, even monitored routinely in the case of air, so that much data are available on their concentrations. But there are several factors that modify these components prior to actual human exposure: We do not breathe air as monitored at an atmospheric sampling station; we may be closer to or farther from the source of lead than is the monitor; we may be inside a building, with or without filtered air; water we drink does not come directly from a stream or river, but often has passed through a chemical treatment plant and a distribution system. A similar type of processing has modified the lead levels present in our food.

Besides the atmospheric lead in environmental components, there are two other industrial components that contribute to this baseline of human exposure: paint pigments and lead solder. Solder contributes directly to the human diet through canned food and copper water distribution systems. Paint and solder are also a source of lead-bearing dusts. The most common dusts in the baseline human environment are street dusts and household dusts. They originate as emissions from mobile or stationary sources, as the oxidation products of surface exposure, or as products of frictional grinding processes. Dusts are different from soil, in that soil derives from crustal rock and typically has a lead concentration of 10-30 μg/g, whereas dusts come from both natural and anthropogenic sources and vary in lead concentration from 1000 to 10,000 μg/g.

The route by which many people receive the largest portion of their daily lead intake is via foods. Several studies have reported average dietary lead intakes in the range of 100-500 μg/day for adults, with individual diets covering a much greater range (Nutrition Foundation, 1982). The sources of lead in plants and animals are air, soil, and untreated waters. Food crops and livestock contain lead in varying proportions from the atmosphere and natural sources. From the farm to the dinner table, lead is added to food as it is harvested, transported, processed, packaged, and prepared. The sources of this lead are dusts of atmospheric and industrial origin, metals used in grinding, crushing, and sieving, solder used in packaging, and water used in cooking. It is assumed that this lead is all of direct atmospheric origin. Direct atmospheric lead can be deposited directly on food materials by dry deposition, or it can be lead in dust that has collected on other surfaces, then transferred to foods. For some of the food items, data are available on lead concentrations just prior to filling of cans. In the case where the food product has not undergone extensive modification (e.g., cooking or added ingredients), the added lead was most likely derived from the atmosphere or from the machinery used to handle the product.

From the time a product is packaged in bottles, cans, or plastic containers until it is opened in the kitchen, it may be assumed that no food item receives atmospheric lead. Most of the lead that is added during this stage comes from the solder used to seal some types of cans. Estimates by the Food and Drug Administration, prepared in cooperation with the National Food Processors Association, suggested that lead in solder contributes more than 66 percent of the lead in canned foods where a lead solder side seam was used. This lead was thought to represent a contribution of 20 percent to the total lead consumption in foods (F.R., 1979, August 31). The contribution of the canning process to overall lead levels in albacore tuna has been reported by Settle and Patterson (1980). The study showed that lead concentrations in canned tuna are elevated above levels in fresh tuna by a factor of 4000. Nearly all of the increase results from leaching of the lead from the soldered seam of the can; tuna from an unsoldered can is elevated by a factor of only 20 compared with tuna fresh from the sea. It is assumed that no further lead is added to food packaged in plastic or paper containers, although there are no data to support or reject this assumption.

Studies that reflect contributions of lead added during kitchen preparation showed that lead in acidic foods stored refrigerated in open cans can increase by a factor of 2-8 in five days if the cans have a lead-soldered side seam not protected by an interior lacquer coating (Capar, 1978). Comparable products in cans with the lacquer coating or in glass jars showed little or no increase.

As a part of its program to reduce the total lead intake by children (0-5 years of age) to less than 100 μg/day by 1988, the U.S. FDA estimated lead intakes for individual children in a large-scale food consumption survey (Beloian and McDowell, 1981). Between 1973 and 1978, intensive efforts were made by the food industry to remove sources of lead from infant food items. By 1980, there had been a 47 percent reduction in the lead concentration of food consumed by children in the age group 0-5 months and a 7 percent reduction for the 6- to 23-month age group. Most of this reduction was accomplished by the removal of soldered cans used for infant formula.

Because the U.S. FDA is actively pursuing programs to decrease lead in adult foods, it is probable that there will be a decrease in total dietary lead consumption over the next decade independent of projected decreases in atmospheric lead concentration. With both sources of lead minimized, the lowest reasonable estimated dietary lead consumption would be 10-15 µg/day for adults and children. This estimate assumes that about 90 percent of the direct atmospheric lead, solder lead, and lead of undetermined origin would be removed from the diet, leaving 8 µg/day from these sources and 3 µg/day of natural and indirect atmospheric lead.

There have been several studies in North America and Europe of the sources of lead in drinking water, and a concentration of 6-8 µg Pb/l is often cited in the literature for specific locations. A recent study in Seattle, WA by Sharrett et al. (1982) showed that the age of the house and the type of plumbing determined the lead concentration in tap water. Lead in standing water from houses newer than five years (copper pipes) averaged 31 µg/l, while houses less than 18 months old averaged about 70 µg/l. Houses older than five years and houses with galvanized pipe averaged less than 6 µg/l. The source of the water supply, the length of the pipe, and the use of plastic pipes in the service line had little or no effect on the lead concentrations. It appears certain that the source of lead in new homes with copper pipes is the solder used to join these pipes, and that this lead is eventually leached away with age.

Ingestion, rather than inhalation, of dust particles appears to be the greater problem in the baseline environmental exposure, especially ingestion during meals and playtime activity by small children. Although dusts are of complex origin, they may be conveniently placed into a few categories relating to human exposure. Generally, the most convenient categories are household dusts, soil dust, street dusts, and occupational dusts. It is a characteristic of dust particles that they accumulate on exposed surfaces and are trapped in the fibers of clothing and carpets. Two other features of dusts are important: first, they must be described in both concentration and amount. For example, the concentration of lead in street dust may be the same in a rural and urban environment, but the amount of dust may differ by a wide margin. Secondly, each category represents some combination of sources. Household dusts contain some atmospheric lead, some paint lead, and some soil lead; street dusts contain atmospheric, soil, and occasionally paint lead. For the baseline human exposure, it is assumed that humans are not exposed to occupational dusts, nor do they live in houses with interior leaded paints. Street dust, soil dust, and some household dust are the primary sources for baseline potential human exposure.

In considering the impact of street dust on the human environment, the obvious question arises as to whether lead in street dust varies with traffic density. It appears that in non-urban environments, lead in street dust ranges from 80 to 130 µg/g, whereas urban street dusts range from 1,000 to 20,000 µg/g. For the purpose of estimating potential human exposure, an average value of 90 µg/g in street dust is assumed for baseline exposure and 1500 µg/g in the discussions of urban environments.

Household dust is also a normal component of the home environment. It accumulates on all exposed surfaces, especially furniture, rugs, and windowsills. Most of the dust values for nonurban household environments fall in the range of 50-500 µg/g. A value of 300 µg/g is assumed. The only natural lead in dust would be some fraction of that derived from soil lead. A value of 10 µg/g seems reasonable, since some of the soil lead is of atmospheric origin. Children ingest about five times as much dust as adults, with most of the excess being street dusts from sidewalks and playgrounds. Exposure to occupational lead by children would be through clothing brought home by parents.

The values for baseline exposure derived or assumed in the preceeding sections are summarized on Table 1-7. These values represent only consumption, not absorption, of lead by the human body.

1.7.6 Additional Exposures

There are many conditions, even in nonurban environments, where an individual may increase his lead exposure by choice, habit, or unavoidable circumstance. These conditions are discussed below as separate exposures to be added as appropriate to the baseline of human exposure described above. Most of these additive effects clearly derive from air or dust; few are from water or food. Ambient air lead concentrations are typically higher in an urban than a rural environment. This factor alone can contribute significantly to the potential lead exposure of Americans through increases in inhaled air and consumed dust. Produce from urban gardens may also increase the daily consumption of lead. Other contributing factors not related only to urban living are houses with interior lead paint or lead plumbing, residences near smelters or refineries, or family gardens grown on high-lead soils. Occupational exposures may also be in an urban or rural setting. These exposures, whether primarily in the occupational environment or secondarily in the home of the worker, would be in addition to other exposures in an urban location or from the special cases of lead-based paint or plumbing.

Urban atmospheres. The fact that urban atmospheres have more airborne lead than nonurban atmospheres contributes not only to lead consumed by inhalation, but to increased amounts of lead in dust as well. Typical urban atmospheres contain 0.5-1.0 µg Pb/m^3. Other variables are the amount of indoor filtered air breathed by urban residents, the amount of time spent indoors, and the amount of time spent on freeways. Dusts vary from 500 to 3000 µg/g in urban environments.

TABLE 1-7. SUMMARY OF BASELINE HUMAN EXPOSURES TO LEAD
(μg/day)

Source	Total lead consumed	Soil: Natural lead consumed	Soil: Indirect atmospheric lead*	Direct atmospheric lead*	Lead from solder or other metals	Lead of undetermined origin
Child-2 yr old						
Inhaled air	0.5	0.001	-	0.5	-	-
Food, Water & beverages	25.1	0.71	1.7	10.3	11.2	1.2
Dust	21.0	0.6	-	19.0	-	1.4
Total	46.6	1.3	1.7	29.8	11.2	2.6
Percent	100%	2.8%	3.5%	64.0%	24.0%	5.6%
Adult female						
Inhaled air	1.0	0.002	-	1.0	-	-
Food, Water & beverages	32.0	0.91	2.4	12.6	8.2	1.5
Dust	4.5	0.2	-	2.9	-	1.4
Total	37.5	1.2	2.5	17.4	13.5	2.9
Percent	100%	3.1%	6.6%	46.5%	36.1%	7.8%
Adult male						
Inhaled air	1.0	0.002	-	1.0	-	-
Food, Water & beverages	45.2	1.42	3.5	19.3	18.9	2.2
Dust	4.5	0.2	-	2.9	-	1.4
Total	50.7	1.6	3.5	23.2	18.9	3.6
Percent	100%	3.1%	6.8%	45.8%	37.2%	7.0%

*Indirect atmospheric lead has been previously incorporated into soil, and will probably remain in the soil for decades or longer. Direct atmospheric lead has been deposited on the surfaces of vegetation and living areas or incorporated during food processing prior to human consumption.

Source: This report.

Houses with interior lead paint. In 1974, the Consumer Product Safety Commission collected household paint samples and analyzed them for lead content (National Academy of Sciences, National Research Council, 1976). The paints with the greatest amounts of lead were typically found in the kitchens, bathrooms, and bedrooms. Peeling and flaking paint contributes to potential human exposure via habitual or inadvertent consumption of paint chips, but powder from painted walls also contributes to the lead concentration of household dust. Flaking paint can also cause elevated lead concentrations in nearby soil. For example, Hardy et al. (1971) measured soil lead levels of 2000 µg/g next to a barn in rural Massachusetts. A steady decrease in lead level with increasing distance from the barn was shown, reaching 60 µg/g at fifty feet from the barn. Ter Haar and Aronow (1974) reported elevated soil lead levels in Detroit near eighteen old wood frame houses painted with lead-based paint. The average soil lead level within two feet of a house was just over 2000 µg/g; the average concentration at ten feet was slightly more than 400 µg/g. The same authors reported smaller soil lead elevations in the vicinity of eighteen brick veneer houses in Detroit. Soil lead levels near painted barns located in rural areas were similar to urban soil lead concentrations near painted houses, suggesting the importance of leaded paint at both urban and rural locations. The baseline lead concentration for household dust of 300 µg/g was increased to 2000 µg/g for houses with interior lead-based paints. The additional 1700 µg/g would add 85 µg Pb/day to the potential exposure of a child. This increase would occur in either an urban or nonurban environment and would be in addition to the urban residential increase if the lead-based painted house were in an urban environment.

Family gardens. Several studies have shown potentially higher lead exposure through the consumption of home-grown produce from family gardens grown on high-lead soils or near sources of atmospheric lead. In family gardens, lead may reach the edible portions of vegetables by direct atmospheric deposition onto aboveground plant parts or onto soil, or by the flaking of lead-containing paint chips from houses. Air concentrations and particle size distributions are the important determinants of deposition to soil or vegetation surfaces. It is unlikely that surface deposition alone can account for more than 2-5 µg/g lead on the surface of a leafy vegetable such as lettuce during a 21-day growing period. It appears that a significant fraction of the lead in both leafy and root vegetables derives from the soil.

Houses with lead plumbing. The Glasgow Duplicate Diet Study (United Kingdom Central Directorate on Environmental Pollution, 1982) reports that children approximately 13 weeks old living in lead-plumbed houses consume 6-480 µg lead/day. Water lead levels in the 131 homes studied ranged from less than 50 to over 500 µg/l. Those children and mothers living in the homes containing high water lead levels generally had greater total lead consumption and higher blood lead levels, according to the study. Breast-fed infants were exposed to much less lead than bottle-fed infants. The results of the study suggest that infants living in lead-plumbed homes may have exposure to considerable amounts of lead. This conclusion was also demonstrated by Sherlock et al. (1982) in a duplicate diet study in Ayr, Scotland.

Residences near smelters and refineries. Air lead concentrations within 2 km of lead smelters and refineries average 5-15 µg/m^3. Considering both inhaled air and dust, a child in this circumstance would be exposed to 1300 µg lead/day above background levels. Exposures to adults would be much less, since they consume only 20 percent of the dusts children consume.

Occupational exposures. The highest and most prolonged exposures to lead are found among workers in the lead smelting, refining, and manufacturing industries (World Health Organization, 1977). In all work areas, the major route of lead exposure is by inhalation and ingestion of lead-bearing dusts and fumes. Airborne dusts settle out of the air onto food, water, the workers' clothing, and other objects, and may be subsequently transferred to the mouth. Therefore, good housekeeping and good ventilation have a major impact on exposure. Even tiny amounts (e.g., 10 mg) of dust containing 100,000 µg lead/g can account for 1,000 µg/day lead exposure.

The greatest potential for high-level occupational exposure exists in the process of lead smelting and refining. The most hazardous operations are those in which molten lead and lead alloys are brought to high temperatures, resulting in the vaporization of lead, because condensed lead vapor or fume has, to a substantial degree, a small (respirable) particle size range.

When metals that contain lead or are protected with a lead-containing coating are heated in the process of welding or cutting, copious quantities of lead in the respirable size range may be emitted. Under conditions of poor ventilation, electric arc welding of zinc silicate-coated steel (containing 4.5 mg lead/cm^2 of coating) produces breathing-zone concentrations of lead reaching 15,000 µg/m^3, far in excess of the current occupational short-term exposure limit in the United States (450 µg/m^3). In a study of salvage workers using oxy-acetylene cutting torches on lead-painted structural steel under conditions of good ventilation, breathing-zone concentrations of lead averaged 1200 µg/m^3 and ranged as high as 2400 µg/m^3.

At all stages in battery manufacture except for final assembly and finishing, workers are exposed to high air lead concentrations, particularly lead oxide dust. Excessive concentrations, as great as 5400 µg/m^3, have been quoted by the World Health Organization (1977). The hazard in plate casting, which is a molten-metal operation, is from the spillage of molten waste products, resulting in dusty floors.

In both the rubber products and the plastics industries, there are potentially high exposures to lead. The potential hazard of the use of lead stearate as a stabilizer in the manufacture of polyvinyl chloride was noted in the 1971 Annual Report of the United Kingdom

Department of Employment, Chief Inspector of Factories (1972). The source of this problem is is the dust that is generated when the lead stearate is milled and mixed with the polyvinyl chloride and the plasticizer. An encapsulated stabilizer that greatly reduces the occupational hazard was reported by Fischbein et al. (1982). Sakurai et al. (1974), in a study of bioindicators of lead exposure, found ambient air concentrations averaging 58 µg/m^3 in the lead-covering department of a rubber hose manufacturing plant.

The manufacture of cans with leaded seams may expose workers to elevated environmental lead levels. Bishop (1980) reports airborne lead concentrations of 25-800 µg/m^3 in several can manufacturing plants in the United Kingdom. Between 23 and 54 percent of the airborne lead was associated with respirable particles. Firing ranges may also be characterized by high airborne lead concentrations; hence, instructors who spend considerable amounts of time in such areas may be exposed to lead. Anderson et al. (1977) discuss plumbism in a 17-year-old male employee of a New York City firing range, where airborne lead concentrations as great as 1000 µg/m^3 were measured during sweeping operations. Removal of leaded paint from walls and other surfaces in old houses may pose a health hazard. Feldman (1978) reports an airborne lead concentration of 510 µg/m^3 after 22 minutes of sanding an outdoor post coated with paint containing 2.5 mg lead/cm^2. After only five minutes of sanding an indoor window sill containing 0.8-0.9 mg lead/cm^2, the air contained 550 µg/m^3. Garage mechanics may also be exposed to excessive lead concentrations. Clausen and Rastogi (1977) report airborne lead levels of 0.2-35.5 µg/m^3 in ten garages in Denmark; the greatest concentration was measured in a paint workshop. Used motor oils were found to contain 1500-3500 µg lead/g, while one brand of gear oil, unused, contained 9280 µg/g. The authors state that absorption through damaged skin could be an important exposure pathway. Other occupations involving risk of lead exposure include stained glass manufacturing and repair, arts and crafts, and soldering and splicing.

Workers involved in the manufacture of both tetraethyl lead and tetramethyl lead, two alkyl lead compounds, are exposed to both inorganic and alkyl lead. The major potential hazard in the manufacture of tetraethyl lead and tetramethyl lead is from skin absorption, but this is guarded against by the use of protective clothing.

Secondary occupational exposure. The amount of lead contained in pieces of cloth 1 cm^2 cut from bottoms of trousers worn by lead workers ranged from 110 to 3,000 µg, with a median of 410 µg. In all cases, the trousers were worn under coveralls. Dust samples from 25 households of smelter workers ranged from 120 to 26,000 µg/g, with a median of 2,400 µg/g.

Special habits or activities. The quantity of food consumed per body weight varies greatly with age and somewhat with sex. A two-year-old child weighing 14 kg eats and drinks 1.5 kg food and water per day. This is 110 g food/kg body wt, or three times the consumption of an 80 kg adult male, who eats 39 g/kg.

Children place their mouths on dust-collecting surfaces and lick non-food items with their tongues. This fingersucking and mouthing activity are natural forms of behavior for young children that expose them to some of the highest concentrations of lead in their environment. A single gram of dust may contain ten times more lead than the total diet of the child.

On the other hand, pica is the compulsive, habitual consumption of non-food items. In the case of paint chips and soil, this habit can present a significant lead exposure for the afflicted person. There are very little data on the amounts of paint or soil eaten by children with varying degrees of pica and exposure can only be expressed on a unit basis. A single chip of paint can represent greater exposure than any other source of lead. For example, Billick and Gray (1978) report lead concentrations of 1000-5000 $\mu g/cm^2$ in lead-based paint pigments. A gram of urban soil may have 150-2000 μg lead.

Lead is also present in tobacco. The World Health Organization (1977) estimates a lead content of 2.5-12.2 μg per cigarette; roughly 2-6 percent of this lead may be inhaled by the smoker. The National Academy of Sciences (1980) has used these data to conclude that a typical urban resident who smokes 30 cigarettes per day may inhale roughly equal amounts of lead from smoking and from breathing urban air. The average adult consumption of table wine in the U.S. is about 12 g/day. Even at 0.1 μg/g, which is ten times higher than drinking water, wine does not appear to represent a significant potential exposure. At one liter/day, however, lead consumption would be greater than the total baseline consumption. McDonald (1981) points out that older wines with lead foil caps may represent a hazard, especially if they have been damaged or corroded. Wai et al. (1979) found the lead content of wine rose from 200 to 1200 μg/liter when the wine was allowed to pass over the thin ring of residue left by the corroded lead foil cap. Newer wines (1971 and later) use other means of sealing.

1.7.7 Summary

Ambient airborne lead concentrations showed no marked trend from 1965 to 1977. Decreases from 1977 to 1982 reflect the smaller lead emissions from mobile sources in recent years. Airborne size distribution data indicate that most of the airborne lead mass is found in submicron particles. Atmospheric lead is deposited on vegetation and soil surfaces, entering the human food chain through contamination of grains and leafy vegetables, of pasture lands, and of soil moisture taken up by all crops. Lead contamination of drinking water supplies appears to originate mostly from within the distribution system.

Environmental contamination by lead should be measured in terms of the total amount of lead emitted to the biosphere. American industry contributes several hundred thousand tons of lead to the environment each year: 61,000 tons from petroleum additives, 44,000 tons from ammunition, 45,000 tons in glass and ceramic products, 16,000 tons in paint pigments, 8,000 tons in food can solder, and untold thousands of tons of captured wastes during smelting, refining, and coal combustion. These are uses of lead which are generally not recoverable; thus, they represent a permanent contamination of the human or natural environment. Although much of this lead is confined to municipal and industrial waste dumps, a large amount is emitted to the atmosphere, waterways, and soil, to become a part of the biosphere.

Potential human exposure can be expressed as the concentrations of lead in those environmental components (air, dust, food, and water) that interface with man. It appears that, with the exception of extraordinary cases of exposure, about 100 μg of lead are consumed daily by each American.

Beyond the baseline level of human exposure, additional amounts of lead consumption are largely a matter of individual choice or circumstance. Most of these additional exposures arise directly or indirectly from atmospheric lead, and in one or more ways probably affect 90 percent of the American population. In some cases, the additive exposure can be fully quantified and the amount of lead consumed can be added to the baseline consumption (Table 1-8). These may be continuous (urban residence) or seasonal (family gardening) exposures. Some factors can be quantified on a unit basis because of wide ranges in exposure duration or concentration. For example, factors affecting occupational exposure are air lead concentrations (10-4000 $\mu g/m^3$), use and efficiency of respirators, length of time of exposure, dust control techniques, and worker training in occupational hygiene.

TABLE 1-8. SUMMARY OF POTENTIAL ADDITIVE EXPOSURES TO LEAD (μg/day)

Exposure	Total lead consumed	Atmospheric lead consumed	Other lead sources
Baseline exposure:			
Child			
Inhaled air	0.5	0.5	-
Food, water & beverages	25.1	10.3	15.6
Dust	21.0	19.0	2.0
Total baseline	46.6	29.7	17.6
Additional exposure due to:			
Urban atmospheres[1]	91	91	
Family gardens[2]	48	12	36
Interior lead paint[3]	110		110
Residence near smelter[4]	880	880	
Secondary occupational[5]	150		
Baseline exposure:			
Adult male			
Inhaled air	1.0	1.0	-
Food, water & beverages	45.2	20.3	34.4
Dust	4.5	2.9	1.6
Total baseline	50.7	24.2	36.0
Additional exposure due to:			
Urban atmospheres[1]	28	28	
Family gardens[2]	120	30	17
Interior lead paint[3]	17		
Residence near smelter[4]	100	100	
Occupational[6]	1100	1100	
Secondary occupational[5]	44		
Smoking[7]	30	27	3
Wine consumption[8]	100	?	?

[1] Includes lead from household (1000 μg/g) and street dust (1500 μg/g) and inhaled air (0.75 $\mu g/m^3$).

[2] Assumes soil lead concentration of 2000 μg/g; all fresh leafy and root vegetables, and sweet corn of Table 7-12 replaced by produce from garden. Also assumes 25% of soil lead is of atmospheric origin.

[3] Assumes household dust rises from 300 to 2000 μg/g. Dust consumption remains the same as baseline.

[4] Assumes household and street dust increase to 10,000 μg/g.

[5] Assumes household dust increases to 2400 μg/g.

[6] Assumes 8-hr shift at 10 $\mu g\ Pb/m^3$ or 90% efficiency of respirators at 100 $\mu g\ Pb/m^3$, and occupational dusts at 100,000 $\mu g/m^3$.

[7] One and a half packs per day.

[8] Assumes unusually high consumption of one liter per day.

1.8 EFFECTS OF LEAD ON ECOSYSTEMS

To function properly, ecosystems require an adequate supply of energy, which continually flows through the systems, and an adequate supply of nutrients, which for the most part, cycle within the ecosystem. There is evidence that lead can interfere with both of these processes. Energy usually enters the ecosystem in the form of sunlight and leaves as heat of respiration. Unlike energy, nutrient and non-nutrient elements are recycled by the ecosystem and transferred from reservoir to reservoir in a pattern usually referred to as a biogeochemical cycle. The reservoirs correspond approximately to the food webs of energy flow (see Figure 1-12). Although elements may enter (e.g., weathering of soil) or leave the ecosystem (e.g., stream runoff), the greater fraction of the available mass of the element is usually cycled within the ecosystem. The boundaries of ecosystems may be as distinct as the border of a pond or as arbitrary as an imaginary circle drawn on a map. Many trace metal studies are conducted in watersheds where some of the boundaries are determined by topography. For atmospheric inputs to terrestrial ecosystems, the boundary is usually defined as the surface of vegetation, exposed rock, or soil. Non-nutrient elements differ little from nutrient elements in their biogeochemical cycles. Quite often, the cycling patterns are similar to those of a major nutrient. In the case of lead, the reservoirs and pathways are very similar to those of calcium.

Atmospheric lead is deposited on the surfaces of soil, vegetation, and water. Lead may also be introduced to natural ecosystems as spent ammunition. In agricultural and other ecosystems more directly influenced by the activities of man, lead may enter as components of fertilizers, pesticides, and paint chips, or by the careless disposal of lead-acid batteries or other industrial products. The movement of lead within ecosystems is influenced by the chemical and physical properties of lead and by the biogeochemical properties of the ecosystem. In the appropriate chemical environment, lead may undergo transformations that affect its solubility (e.g., formation of lead sulfate in soils), its bioavailability (e.g., chelation with humic substances), or its toxicity (e.g., chemical methylation).

In prehistoric times, the contribution of lead from weathering of soil was probably about 4g/ha·yr and, from atmospheric deposition, about 0.02 g/ha·yr. Weathering rates are presumed to have remained the same, but atmospheric inputs are believed to have increased to 180 g/ha·yr in natural and some cultivated ecosystems, and up to 3000 g/ha·yr in urban ecosystems and along roadways. There is, however, wide variation in the amount of lead transferred from the atmosphere to terrestrial ecosystems. For example, Elias et al. (1976) found 15 g/ha·yr in a remote subalpine ecosystem of California; Lindberg and Harriss (1981) found 150 g/ha·yr in the Walker Branch watershed of Tennessee; Smith and Siccama (1981) report 270 g/ha·yr in the Hubbard Brook forest of New Hampshire; Getz et al. (1977c) estimated 240 g/ha·yr by wet

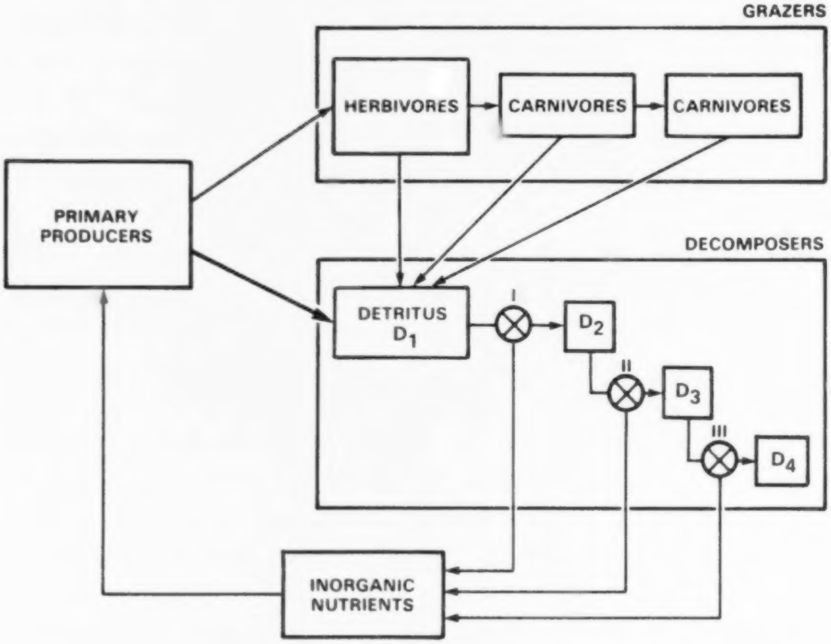

Figure 1-12. This figure depicts cycling processes within the major components of a terrestrial ecosystem, i.e. primary producers, grazers and decomposers. Nutrient and non-nutrient elements are stored in reservoirs within these components. Processes that take place within reservoirs regulate the flow of elements between reservoirs along established pathways. The rate of flow is in part a function of the concentration in the preceding reservoir. Lead accumulates in decomposer reservoirs (D_1-D_4) which have a high binding capacity for this metal. When the flow of nutrients is reduced at I, II, or III, the rate of flow of inorganic nutrients to primary producers is reduced.

Source: Adapted from Swift et al. (1979).

precipitation alone in a rural ecosystem largely cultivated, and 770 g/ha·yr in an urban ecosystem; Jackson and Watson (1977) found 1,000,000 g/ha·yr near a smelter in southeastern Missouri. Factors causing great variation are remoteness from source (leading to lower air concentrations, difference in particle size, and greater dependence on wind as a mechanism of deposition) and type of vegetation cover. For example, deciduous leaves may, by the nature of their surface and orientation in the wind stream, be more suitable deposition surfaces than conifer needles.

Many of the effects of lead on plants, microorganisms, and ecosystems arise from the fact that lead from atmospheric and weathering inputs is retained by soil. (One effect of cultivation is that atmospheric lead is mixed to a greater depth than the 0-5 cm of natural soils). Although no firm documentation exists, it is reasonable to assume from the known chemistry of lead in soil that other metals may be displaced from binding sites on organic matter and that the chemical breakdown of inorganic soil fragments may be retarded by the interference of lead with the action of fulvic acid on iron bearing crystals. Soil cation exchange capacity, a major factor, is determined by the relative size of the clay and organic fractions, soil pH, and the amount of Fe-Mn oxide films present (Nriagu, 1978a). Of these, organic humus and high soil pH are the dominant factors in immobilizing lead. Under natural conditions, most of the total lead in soil would be tightly bound within the crystalline structure of inorganic soil fragments, unavailable to soil moisture. Available lead, bound on clays, organic colloids, and Fe-Mn films, would be controlled by the slow release of bound lead from inorganic rock sources. Because lead is strongly immobilized by humic substances, only a small fraction (perhaps 0.01 percent in soils with 20 percent organic matter, pH 5.5) is released to soil moisture.

In soils with lead concentrations within the range of natural lead (15-30 μg/g), only trace amounts of lead are absorbed by plants. The amount absorbed increases when the concentration of lead in soil increases or when the binding capacity of soil for lead decreases. Uptake by root systems does not necessarily mean the lead reaches the stems, leaves or fruits. Rather, the process should be seen as a soil-plant continuum that strongly favors retention of lead by the soil and the root system.

The soil-root continuum is a complex structure that consists of the soil particles, the soil solution, the mutigel or other remnants of root exudates, the epidermal cells with elongated root hairs, and the root cortical cells. The walls of the epidermal cells are a loose matrix of cellulose and hemicellulose fibers. Much of this continuum is of biological origin and contains compounds active in ion exchange, such as hemicelluloses and pectic substances that are heavily endowed with -COOH groups, and proteins that also have charged groups. As a cation moves from the soil particle to the root cortex, whether by mass flow or diffusion, it is continually proximate to root structures with a high binding capacity. Lead is more tightly bound at these sites than other cations, even calcium. Consequently, relatively little lead passes through the roots into the shoot. It appears that most of the soil lead is retained within the root. However, some plants may allow more lead to translocate than others.

Hutchinson (1980) has reviewed the effects of acid precipitation on the ability of soils to retain cations. Excess calcium and other metals are leached from the A horizon of soils by rain with a pH more acidic than 4.5. Most soils in the eastern United States are normally acidic (pH 3.5-5.2) and the leaching process is a part of the complex equilibrium maintained in the soil system. By increasing the leaching rate, acid rain can reduce the availability of nutrient metals to organisms dependent on the top layer of soil. It appears that acidification of soil may increase the rate of removal of lead from the soil, but not before several major nutrients are removed first. The effect of acid rain on the retention of lead by soil moisture is not known.

Atmospheric lead may enter aquatic ecosystems by wet or dry deposition or by the erosional transport of soil particles. In waters not polluted by industrial, agricultural, or municipal effluents, the lead concentration is usually less than 1 µg/l. Of this amount, approximately 0.02 µg/l is natural lead and the rest is anthropogenic lead, probably of atmospheric origin (Patterson, 1980). Surface waters mixed with urban effluents may frequently reach lead concentrations of 50 µg/l, and occasionally higher. In still water, lead is removed from the water column by the settling of lead-containing particulate matter, by the formation of insoluble complexes, or by the adsorption of lead onto suspended organic particles. The rate of sedimentation is determined by temperature, pH, oxidation-reduction potential, ionic competition, the chemical form of lead in water, and certain biological activities (Jenne and Luoma, 1977). In the sediments of streams, rivers, and lakes, lead appears to be immobile, in the sense that it is not easily transported by redissolution in fresh water.

1.8.1 Effects on Plants

Some physiological and biochemical effects of lead on vascular plants have been detected under laboratory conditions at concentrations higher than those normally found in the environment. The commonly reported effects are the inhibition of photosynthesis, respiration, or cell elongation, all of which reduce the growth of the plant (Koeppe, 1981). Lead may also induce premature senescence, which may affect the long-term survival of the plant or the ecological success of the plant population. Most of the lead in or on a plant occurs on the surfaces of leaves and the trunk or stem. The surface concentration of lead in trees, shrubs, and grasses usually exceeds the internal concentration by a factor of at least five (Elias et al, 1978). The major effect of surface lead at ambient concentrations seems to be on subsequent components of the grazing food chain and on the decomposer food chain following litterfall (Elias et al., 1982).

Two defensive mechanisms appear to exist in the roots of plants for removing lead from the stream of nutrients flowing to the above-ground portions of plants. Lead may be deposited with cell wall material exterior to the individual root cells, or may be sequestered in organelles within the root cells. Any lead not captured by these mechanisms would likely move with nutrient metals from cell to cell through the symplast and into the vascular system. Uptake of lead by plants may be enhanced by symbiotic associations with mycorrhizal fungi. The three primary factors that control the uptake of nutrients by plants are the following: (1) the surface area of the roots; (2) the ability of the root to absorb particular ions; and (3) the transfer of ions through the soil. The symbiotic relationship between mycorrhizal fungi and the roots of higher plants can increase the uptake of nutrients by enhancing all three of these factors.

The translocation of lead to aboveground portions of the plant is not clearly understood. Lead may follow the same pathway and be subject to the same controls as a nutrient metal such as calcium. There may be several mechanisms that prevent the translocation of lead to other plant parts. The primary mechanisms may be storage in cell organelles or adsorption on cell walls. Some lead passes into the vascular tissue, along with water and dissolved nutrients, and is carried to physiologically active tissue of the plant. Evidence that lead in contaminated soils can enter the vascular system of plants and be transported to aboveground parts may be found in the analysis of tree rings. These chronological records confirm that lead can be translocated in proportion to the concentrations of lead in soil.

Because most of the physiologically active tissue of plants is involved in growth, maintenance, and photosynthesis, it is expected that lead might interfere with one or more of these processes. Indeed, such interferences have been observed in laboratory experiments at lead concentrations greater than those normally found in the field, except near smelters or mines (Koeppe, 1981). Inhibition of photosynthesis by lead may be by direct interference with the light reaction or the indirect interference with carbohydrate synthesis. Miles et al. (1972) demonstrated substantial inhibition of photosystem II near the site of water splitting, a biochemical process believed to require manganese. Devi Prasad and Devi Prasad (1982) found a 10 percent inhibition of pigment production in three species of green algae at a lead concentration of 1 μg/g, increasing to 50 percent inhibition at 3 μg/g. Bazzaz et al. (1974, 1975) observed reduced net photosynthesis that may have been caused indirectly by lead inhibiting carbohydrate synthesis.

The stunting of plant growth may be by the inhibition of the growth hormone IAA (indole-3-ylacetic acid) by lead. Lane et al. (1978) found that 10 µg/g lead as lead nitrate in the nutrient medium of wheat coleoptiles produced a 25 percent reduction in elongation. Lead may also interfere with plant growth by reducing respiration or inhibiting cell division. Miller and Koeppe (1971) and Miller et al. (1975) showed succinate oxidation inhibition in isolated mitochondria as well as stimulation of exogenous NADH oxidation with related mitochondrial swelling.

Hassett et al. (1976), Koeppe (1977), and Malone et al. (1978) described significant inhibition by lead of lateral root initiation in corn. The interaction of lead with calcium has been shown by several authors, most recently by Garland and Wilkins (1981), who demonstrated that barley seedlings (Hordeum vulgare), which were growth inhibited at 2 µg lead/g sol. with no added calcium, grew at about half the control rate with 17 µg calcium/g sol. This relation persisted up to 25 µg lead/g sol. and 500 µg calcium/g sol.

These studies of the physiological effects of lead on plants all show some effect at concentrations of 2-10 µg/g in the nutrient medium of hydroponically-grown agricultural plants. It is certain that no effects would have been observed at these concentrations had the lead solutions been added to normal soil, where the lead would have been bound by humic substances. There is no firm relationship between soil lead and soil moisture lead because each soil type has a unique capacity to retain lead and to release that lead to the soil moisture film surrounding the soil particle. Once in soil moisture, lead seems to pass freely to the plant root according to the capacity of the plant root to absorb water and dissolved substances.

Some plant species have developed populations tolerant to high lead soils. Using populations taken from mine waste and uncontaminated control areas, some authors have quantified the degree of tolerance of Agrostis tenuis (Karataglis, 1982) and Festuca rubra (Wong, 1982) under controlled laboratory conditions. Root elongation was used as the index of tolerance. At lead concentrations of 36 µg/g nutrient solution, all populations of A. tenuis were completely inhibited. At 12 µg/g, the control populations from low-lead soils were completely inhibited, but the populations from mine soils achieved 30 percent of their normal growth (growth at no lead in nutrient solution). At 6 µg/g, the control populations achieved 10 percent of their normal growth, and tolerant populations achieved 42 percent. There were no measurements of lead below 6 µg/g.

The plant effect studies support the conclusion that inhibition of plant growth begins at a lead concentration of less than 1 µg/g soil moisture and becomes completely inhibitory at a level between 3 and 10 µg/g. Plant populations that are genetically adapted to high lead soils may achieve 50 percent of their normal root growth at lead concentrations above 3 µg/g.

Even under the best of conditions where soil has the highest capacity to retain lead, most plants would experience reduced growth rate (inhibition of photosynthesis, respiration, or cell elongation) in soils containing 10,000 μg lead/g or greater. Concentrations approaching this value typically occur around smelters and near major highways. These conclusions pertain to soil with the ideal composition and pH to retain the maximum amount of lead. Acid soils or soils lacking organic matter would inhibit plants at much lower lead concentrations.

1.8.2 Effects on Microorganisms

It appears that microorganisms are more sensitive than plants to soil lead pollution and that changes in the composition of bacterial populations may be an early indication of lead effects. Delayed decomposition may occur at lead concentrations of 750 μg/g soil and nitrification inhibition at 1000 μg/g.

Tyler (1972) explained three ways in which lead might interfere with the normal decomposition processes in a terrestrial ecosystem. Lead may be toxic to specific groups of decomposers, it may deactivate enzymes excreted by decomposers to break down organic matter, or it may bind with the organic matter to render it resistant to the action of decomposers. Because lead in litter may selectively inhibit decomposition by soil bacteria at concentrations of 2000-5000 μg/g, forest floor nutrient cycling processes may be seriously disturbed near lead smelters. This is especially important because approximately 70 percent of plant biomass enters the decomposer food chain. If decomposition of the biomass is inhibited, then much of the energy and nutrients remain unavailable to subsequent components of the food chain. There is also the possibility that the ability of soil to retain lead would be reduced, as humic substances are byproducts of bacterial decomposition. Because they are interdependent, the absence of one decomposer group in the decomposition food chain seriously affects the success of subsequent groups, as well as the rate at which plant tissue decomposes. Each group may be affected in a different way and at different lead concentrations. Lead concentrations toxic to decomposer microbes may be as low as 1-5 μg/g or as high as 5000 μg/g. Under conditions of mild contamination, the loss of one sensitive bacterial population may result in its replacement by a more lead-tolerant strain. Delayed decomposition has been reported near smelters, mine waste dumps, and roadsides. This delay is generally in the breakdown of litter from the first stage (0_1) to the second (0_2), with intact plant leaves and twigs accumulating at the soil surface. The substrate concentrations at which lead inhibits decomposition appear to be very low.

The conversion of ammonia to nitrate in soil is a two-step process mediated by two genera of bacteria, Nitrosomonas and Nitrobacter. Nitrate is required by all plants, although some maintain a symbiotic relationship with nitrogen-fixing bacteria as an alternate source of nitrogen. Those which do not would be affected by a loss of free-living nitrifying bacteria, and it is known that many trace metals inhibit this nitrifying process. Lead is the least of these, inhibiting nitrification 14 percent at concentrations of 1000 μg/g soil. Even a 14 percent inhibition of nitrification can reduce the potential success of a plant population, as nitrate is usually the limiting nutrient in terrestrial ecosystems.

1.8.3 Effects on Animals

Forbes and Sanderson (1978) have reviewed reports of lead toxicity in domestic and wild animals. Lethal toxicity can usually be traced to consumption of lead battery casings, lead-based paints, oil wastes, putty, linoleum, pesticides, lead shot, or forage near smelters. Awareness of the routes of uptake is important in interpreting the exposure and accumulation in vertebrates. Inhalation rarely accounts for more than 10-15 percent of the daily intake of lead (National Academy of Sciences, 1980); food is the largest contributor of lead to animals. The type of food an animal eats determines the rate of lead ingestion. In the case of herbivores, more than 90 percent of the total lead in leaves and bark may be surface deposition, but relatively little surface deposition may be found on some fruits, berries, and seeds that have short exposure times; roots intrinsically have no surface deposition. Similarly, ingestion of lead by a carnivore depends mostly on deposition on herbivore fur and somewhat less on lead in herbivore tissue.

The type of food eaten is a major determinant of lead body burdens in small mammals. Goldsmith and Scanlon (1977) and Scanlon (1979) measured higher lead concentrations in insectivorous species than in herbivorous species, confirming the earlier work of Quarles et al. (1974) which showed body burdens of granivores<herbivores<insectivores, and Jeffries and French (1972) that granivores<herbivores. Among the herbivorous groups, sucking insects have lower lead concentrations than chewing insects, especially in regions near roadsides, where more lead is found on vegetation surfaces. Williamson and Evans (1972) found that gradients away from roadsides are not the same as with vertebrates, in that invertebrate lead decreases more slowly than vertebrate lead relative to decreases in soil lead. In _Cepaea_ _hortensis_, a terrestrial snail, Williamson (1979) found most of the lead in the digestive gland and gonadal tissue. A continuation of the study (Williamson, 1980) showed that body weight, age, and daylength influenced the lead concentrations in soft tissues. Beeby and Eaves (1983) addressed the question of whether uptake of lead in the garden snail, _Helix_ _aspersa_, is related to the nutrient requirement for calcium during shell formation and reproductive activity. They found both metals were strongly correlated with changes in dry weight and little evidence for correlation of lead with calcium, independent of weight gain or loss.

Gish and Christensen (1973) found lead in whole earthworms to be correlated with soil lead, with little rejection of lead by earthworms. Consequently, animals feeding on earthworms from high-lead soils might receive toxic amounts of lead in their diets, although there was no evidence of toxic effects on the earthworms. Ash and Lee (1980) cleared the digestive tracts of earthworms and still found direct correlation of lead in earthworms with soil lead; in this case, soil lead was inferred from fecal analyses. Ireland and Richards (1977) also found some localization of lead in subcellular organelles of the chloragogue and intestinal tissue. In view of the fact that chloragocytes are believed to be involved with waste storage and glycogen synthesis, the authors concluded that this tissue is used to sequester lead in the manner of vertebrate livers.

Chmiel and Harrison (1981) showed that the bones of small mammals had the highest concentrations of lead, with kidneys and livers somewhat less. They also showed greater bone concentrations in insectivores than herbivores, both at control and contaminated sites. Clark (1979) found lead concentrations in shrews, voles, and brown bats from roadside habitats near Washington, D.C., to be higher than any previously reported. There are few studies reporting lead in vertebrate tissues from remote sites. Elias et al. (1976, 1982) reported tissue concentrations in voles, shrews, chipmunks, tree squirrels, and pine martens from the remote High Sierra. Bone concentrations were generally only 2 percent of those reported from roadside studies and 10 percent of the controls of roadside studies, indicating that the controls in the roadside studies were themselves contaminated to a large degree.

While it is impossible to establish a safe limit of daily lead consumption, it is reasonable to generalize that a regular diet of 2-8 mg lead/kg·day body weight over an extended period of time (Botts, 1977) will cause death in most animals. Animals of the grazing food chain are affected most directly by the accumulation of aerosol particles on vegetation surfaces, and somewhat indirectly by the uptake of lead through plant roots. Many of these animals consume more than 1 mg lead/kg·day in habitats near smelters and roadsides, but no toxic effects have been documented. Animals of the decomposer food chain are affected indirectly by lead in soil, which can eliminate populations of microorganisms preceeding animals in the food chain or occupying the digestive tract of animals and aiding in the breakdown of organic matter. Invertebrates may also accumulate lead at levels toxic to their predators.

Borgmann et al. (1978) found increased mortality in a freshwater snail, Lymnaea palutris, associated with stream water with a lead content as low as 19 µg/l. Full life cycles were studied to estimate population productivity. Although individual growth rates were not affected, increased mortality, especially at the egg hatching stage, effectively reduced total biomass production at the population level. Production was 50 percent at a lead concentration of 36 µg/l and 0 percent at 48 µg/l.

Aquatic animals are affected by lead at water concentrations lower than previously considered safe (50 µg/l) for wildlife. These concentrations occur commonly, but the contribution of atmospheric lead to specific sites of high aquatic lead is not clear. Hematological and neurological responses are the most commonly reported effects of extended lead exposures in aquatic vertebrates. Hematological effects include the disabling and destruction of mature erythrocytes and the inhibition of the enzyme ALA-D required for hemoglobin synthesis. At low exposures, fish compensate by forming additional erythrocytes, which often do not reach maturity; at higher exposures, the fish become anemic. Symptoms of neurological responses are difficult to detect at low exposure, but higher exposure can induce neuromuscular distortion, anorexia, and muscle tremors. Spinal curvature eventually occurs with time or increased concentration.

1.8.4 Effects on Ecosystems

Recent studies have shown three areas of concern where the effects of lead on ecosystems may be extremely sensitive. First, decomposition is delayed by lead, as some decomposer microorganisms and invertebrates are inhibited by soil lead. Secondly, some ecosystems experience subtle shifts toward lead-tolerant plant populations. Thirdly, the natural processes of calcium biopurification are circumvented by the accumulation of lead on the surfaces of vegetation and in the soil reservoir. These problems all arise because lead in ecosystems is deposited on vegetation surfaces, accumulates in the soil reservoir, and is not removed with the surface and ground water passing out of the ecosystem.

Terrestrial ecosystems, especially forests, accumulate a tremendous amount of cellulose as woody tissue of trees. Few animals can digest cellulose and most of these require symbiotic associations with specialized bacteria. It is no surprise then, that most of this cellulose must eventually pass through the decomposer food chain. Because 80 percent or more of net primary production passes through the decomposing food chain, the energy of this litter is vital to the rest of the plant community and the inorganic nutrients are vital to plants.

Babich et al. (1983) introduced the concept of ecological dose as it applies to the effects of metals on ecological processes in soil. The inhibition of microbe-mediated processes can be used to quantify the effects of environmental pollutants on natural ecosystems. The ecological dose of 50 percent (EcD_{50}) is the concentration of a toxicant that inhibits a microbe-mediated ecologic process by 50 percent. Since microbes are an integral part of the biogeochemical cycling of elements and the flow of energy through an ecosystem, they are an important indicator of the productivity of the ecosystem. This concept is superior to the lethal dose (LD) concept because it is based on an assemblage of heterogeneous populations that are important to the ecosystem and that might be comparable to similar population assemblages of other ecosystems. The LD concept relies on the elimination of single population that may be insignificant to the ecosystem or not comparable to other ecosystems.

The amount of lead that causes litter to be resistant to decomposition is not known. Doelman and Haanstra (1979) demonstrated the effects of soil lead content on delayed decomposition: sandy soils lacking organic complexing compounds showed a 30 percent inhibition of decomposition at 750 µg/g, including the complete loss of major bacterial species, whereas the effect was reduced in clay soils and non-existent in peat soils. Organic matter maintains the cation exchange capacity of soils. A reduction in decomposition rate was observed by Doelman and Haanstra (1979) even at the lowest experimental concentration of lead, leading to the conclusion that some effect might have occurred at even lower concentrations.

When decomposition is delayed, the availability of nutrients may be limited for plants. In tropical regions or areas with sandy soils, rapid turnover of nutrients is essential for the success of the forest community. Even in a mixed deciduous forest, a significant portion of the nutrients, especially nitrogen and sulfur, may be found in the litter reservoir (Likens et al. 1977). Annual litter inputs of calcium and nitrogen to the soil account for about 60 percent of root uptake. With delayed decomposition, plants must rely on precipitation and soil weathering for the bulk of their nutrients. Furthermore, the organic content of soil may decrease, reducing the cation exchange capacity of soil.

It has been observed that plant communities near smelter sites are composed mostly of lead-tolerant plant populations. In some cases, these populations appear to have adapted to high lead soils, since populations of the same species from low lead soils often do not thrive on high lead soils. In some situations, it is clear that soil lead concentration has become the dominant factor in determining the success of plant populations and the stability of the ecological community.

Biopurification is a process that regulates the relative concentrations of nutrients versus non-nutrient elements in biological components of a food chain. In the absence of absolute knowledge of natural lead concentrations, biopurification can be a convenient method for estimating the degree of contamination. It is now believed that calcium reservoirs in members of grazing and decomposer food chains were contaminated by factors of 30-500, i.e., that 97-99.9 percent of the lead in organisms is of anthropogenic origin. Burnett and Patterson (1980) have shown a similar pattern for a marine food chain.

Ecosystem inputs of lead by the atmospheric route have established new pathways and widened old ones. Insignificant amounts of lead are removed by surface runoff or ground water seepage. It is likely that the ultimate fate of atmospheric lead will be a gradual elevation in lead concentration of all reservoirs in the system, with most of the lead accumulating in the detrital reservoir. Because there is no protection from industrial lead once it enters the atmosphere, it is important to fully understand the effects of industrial lead emissions.

Of the 450,000 metric tons emitted annually on a global basis, 115,000 metric tons of lead fall on terrestrial ecosystems. Evenly distributed, this would amount to 0.1 g/ha·yr, which is much lower than the range of 15-1,000,000 g/ha·yr reported in ecosystem studies in the United States. Consequently, it is apparent that lead has permeated these ecosystems and accumulated in the soil reservoir, where it will remain for decades. Within 20 meters of every major highway, up to 10,000 µg lead have been added to each gram of surface soil since 1930 (Getz et al., 1977b). Near smelters, mines, and in urban areas, as much as 130,000 µg/g have been observed in the upper 2.5 cm of soil (Jennett et al., 1977). At increasing distances up to 5 km away from sources, the gradient of lead added since 1930 drops to less than 10 µg/g (Page and Ganje, 1970), and 1-5 µg/g have been added in regions more distant than 5 km (Nriagu, 1978a). In undisturbed ecosystems, atmospheric lead is retained by soil organic matter in the upper layer of soil surface. In cultivated soils, this lead is mixed with soil to a depth of 25 cm.

The ability of an ecosystem to compensate for atmospheric lead inputs, especially in the presence of other pollutants such as acid precipitation, depends not so much on factors of ecosystem recovery, but on undiscovered factors of ecosystem stability. Recovery implies that inputs of the perturbing pollutant have ceased and that the pollutant is being removed from the ecosystem. In the case of lead, the pollutant is not being eliminated from the system nor are the inputs ceasing. Terrestrial ecosystems will never return to their original, pristine levels of lead concentrations.

1.9 QUANTITATIVE EVALUATION OF LEAD AND BIOCHEMICAL INDICES OF LEAD EXPOSURE IN PHYSIOLOGICAL MEDIA

A complete understanding of a toxic agent's biological effects (including any statement of dose-effect relationships) requires quantitative measurement of either that agent in some biological medium or a physiological parameter associated with exposure to the agent. Quantitative analysis involves a number of discrete steps, all of which contribute to the overall reliability of the final analytical result: sample collection and shipment, laboratory handling, instrumental analysis, and criteria for internal and external quality control.

From a historical perspective, the definition of "satisfactory analytical method" for lead has been changing steadily as new and more sophisticated equipment has become available and understanding of the hazards of pervasive contamination along the analytical course has increased. The best example of this change is the current use of the definitive method for lead analysis, isotope-dilution mass spectrometry, in conjunction with "ultra-clean" facilities and sampling methods, to demonstrate conclusively not only the true extent of anthropogenic input of lead to the environment over the years but also the relative limitations of most of the methods used today for lead measurement.

1.9.1 Determinations of Lead in Biological Media

The low levels of lead in biological media, even in the face of excessive exposure, and the fact that sampling of such media must be done against a backdrop of pervasive lead contamination necessitates that samples be collected and handled carefully. Blood lead sampling is best done by venous puncture and collection into low-lead tubes after careful cleaning of the puncture site. The use of finger puncture as an alternative method of sampling should be avoided, if feasible, given the risk of contamination associated with the practice in industrialized areas. While collection of blood onto filter paper enjoyed some popularity in the past, paper deposition of blood requires special correction for hematocrit/hemoglobin level.

Urine sample collection requires the use of lead-free containers as well as addition of a bactericide. If feasible, 24-hr sampling is preferred to spot collection. Deciduous teeth vary in lead content both within and across type of dentition. Thus, a specific tooth type should be uniformly obtained for all study subjects and, if possible, more than a single sample should be obtained from each subject.

Many reports over the years have purported to offer satisfactory analysis of lead in blood and other biological media, often with severe inherent limitations on accuracy and precision, meager adherence to criteria for accuracy and precision, and a limited utility across a spectrum of analytical applications. Therefore, it is only useful to discuss "definitive" and, comparatively speaking, "reference" methods presently used.

In the case of lead in biological media, the definitive method is isotope-dilution mass spectrometry (IDMS). The accuracy and unique precision of IDMS arise from the fact that all manipulations are on a weight basis involving simple procedures, and measurements entail only lead isotope ratios and not the absolute determinations of the isotopes involved, which greatly reduces instrumental corrections and errors. Reproducible results to a precision of one part in 10^4-10^5 are routine with appropriately designed and competently operated instrumentation. Although this methodology is still not recognized in many laboratories, it was the first breakthrough, in tandem with "ultra-clean" procedures and facilities, in definitive methods for indexing the progressive increase in lead contamination of the environment over the centuries. Given the expense, required level of operator expertise, and time and effort involved for measurements by IDMS, this methodology mainly serves for analyses that either require extreme accuracy and precision, e.g., geochronometry, or for the establishment of analytical reference material for general testing purposes or the validation of other methodologies.

While the term "reference method" for lead in biological media cannot be rigorously applied to any procedures in popular use, the technique of atomic absorption spectrometry (AAS) in its various configurations, or the electrochemical method, anodic stripping voltammetry (ASV), come closest to meriting the designation. Other methods that are generally applied in metal analyses are either limited in sensitivity or are not feasible for use on theoretical grounds for lead analysis.

Measurement of Lead in Blood. Atomic absorption spectrometry, as applied to analysis of whole blood, generally involves flame or flameless micromethods. One macromethod, the Hessel procedure, still enjoys some popularity. The Delves cup procedure, which employes flame microanalysis, can be applied to blood lead with an apparent operational sensitivity of about 10 μg/dl blood and a relative precision of approximately 5 percent in the range of blood lead seen in populations in industrialized areas. The flameless, or electrothermal, method of AAS enhances sensitivity about tenfold, but precision can be more problematic because of chemical and spectral interferences.

The most widely used and sensitive electrochemical method for lead in blood is ASV. For most accurate results, chemical wet-ashing of samples must be carried out, although this process is time consuming and requires the use of lead-free reagents. Metal exchange reagents have been employed in lieu of the ashing step to liberate lead from binding sites, although this substitution is associated with less precision. For the ashing method, relative precision is approximately 5 percent; in terms of accuracy and sensitivity, problems appear at low lead levels, e.g., 5 μg/dl or below, particularly if samples contain elevated copper levels.

Lead in Plasma. Since lead in whole blood is virtually all confined to the erythrocyte, plasma levels are quite low and extreme care must be employed to measure plasma levels reliably. The best method for such measurement is IDMS, employed in an ultra-clean facility. Atomic absorption spectrometry (AAS) is satisfactory for comparative analyses across a range of relatively high whole blood values.

Lead in Teeth. Lead measurement in teeth has involved either whole tooth sampling or analysis of specific regions such as dentine or circumpulpal dentine. In either case, samples must be solubilized after careful surface cleaning to remove contamination; solubilization is usually accompanied by either wet-ashing directly or ashing subsequent to a dry-ashing step.

Atomic absorption spectrometry and ASV have been employed more frequently for such determinations than any other method. With AAS, the high mineral content of teeth argues for preliminary isolation of lead via chelation/extraction. The relative precision of analysis for within-run measurement is around 5-7 percent, with the main determinant of variance in regional assay being the initial isolation step. One change from the usual methods for such measurement is the *in situ* measurement of lead by X-ray fluorescence spectrometry in children.

Lead measured in this fashion allows observation of ongoing lead accumulation, rather than waiting for exfoliation.

Lead in Hair. The analysis of lead in hair as an exposure indicator offers the advantages of being a noninvasive procedure that uses a medium of indefinite stability. However, there is still the crucial problem of external surface contamination, which is such that it is still not possible to state that any cleaning protocol reliably differentiates between externally and internally deposited lead.

Studies that demonstrate a correlation between increasing hair lead and increasing severity of a measured effect probably support arguments for using hair as an external indicator of exposure. However, such measurement using cleaning protocols that have not been independently validated will overstate the relative accumulation of "internal" hair lead in terms of some endpoint and will also underestimate the relative sensitivity of changes in internal lead content with exposure. One consequence of this would be, for example, an apparent threshold for a given effect in terms of hair lead which is significantly above the actual threshold. Because of these concerns, the analysis of hair lead is best used with the simultaneous measurement of blood lead.

Lead in Urine. The analysis of lead in urine is complicated by the relatively low levels of the element in this medium, as well as the complex mixture of other mineral elements present. Urine lead levels are most useful and also somewhat easier to determine in cases of chelation mobilization or chelation therapy, where levels are high enough to permit good precision and dilution of matrix interference.

Samples are probably best analyzed by prior chemical wet-ashing, using the usual mixture of acids. Both ASV and AAS have been applied to urine analysis, with the latter more routinely used and usually with a chelation/extraction step.

Lead in Other Tissues. Bone samples require cleaning procedures for removal of muscle and connective tissue and chemical solubilization prior to analysis. Methods of analysis are comparatively limited and flameless AAS is the technique of choice.

In vivo lead measurements in bone have been reported with lead workers using X-ray fluorescence analysis and a radioisotopic source for excitation. One problem with this approach with moderate lead exposure is the detection limit, which is approximately 20 ppm. Soft organ analysis poses a problem in terms of heterogeneity in lead distribution within an organ (e.g., brain and kidney). In such cases, regional sampling or homogenization must be carried out. Both flame and flameless AAS appear to be satisfactory for soft tissue analysis and are the most widely used analytical methods.

Quality Assurance Procedures in Lead Analyses. In terms of available information, the major focus in establishing quality control protocols for lead has involved whole blood measurements. Translated into practice, quality control revolves around steps employed within the laboratory, using a variety of internal checks, and the further reliance on external checks, such as a formal continuing multi-laboratory proficiency testing program.

Within the laboratory, quality assurance protocols can be divided into start-up and routine procedures. The former involves establishment of detection limits, within-run and between-run precision, analytical recovery, and comparison with some reference technique within or outside the laboratory. The reference method is assumed to be accurate for the particular level of lead in some matrix at a particular point in time. Correlation with such a method at a satisfactory level, however, may simply indicate that both methods are equally inaccurate but performing with the same level of precision proficiency. More preferable is the use of certified samples having lead at a level established by the definitive method.

For blood lead, the Centers for Disease Control (CDC) periodically survey overall accuracy and precision of methods used by reporting laboratories. In terms of overall accuracy and precision, one such survey found that ASV, as well as the Delves cup and extraction variations of AAS, performed better than other procedures. These results do not mean that a given laboratory cannot perform better with a particular technique; rather, such data are of assistance for new facilities choosing among methods.

Of particular value to laboratories carrying out blood lead analyses are the external quality assurance programs at both the State and Federal levels. The most comprehensive proficiency testing program is that carried out by the CDC. This program actually consists of two subprograms, one directed at facilities involved in lead poisoning prevention and screening (Center for Environmental Health) and the other concerned with laboratories seeking certification under the Clinical Laboratories Improvement Act of 1967, as well as under regulations of the Occupational Safety and Health Administration's (OSHA) Laboratory Improvement Program Office. Judging from the relative overall improvements in reporting laboratories over the years of the programs' existence, the proficiency testing programs have served their purpose well. In this regard, OSHA criteria for laboratory certification require that eight of nine samples be analyzed correctly for the previous quarter. This level of required proficiency reflects the ability of a number of laboratories to actually perform at this level.

1.9.2 Determination of Biochemical Indices of Lead Exposure in Biological Media

Determination of Erythrocyte Porphyrin (Free Erythrocyte Protoporphyrin, Zinc Protoporphyrin). With lead exposure, erythrocyte protoporphyrin IX accumulates because of impaired placement of divalent iron to form heme. Instead, divalent zinc occupies the place of the native iron. Depending upon the method of analysis, either metal-free erythrocyte porphyrin (EP) or zinc protoporphyrin (ZPP) is measured, the former arising from loss of zinc in the chemical manipulation. Virtually all methods now in use for EP analysis exploit the ability of the porphyrin to undergo intense fluorescence when excited by ultraviolet light. Such fluorometric methods can be further classified as wet chemical micromethods or direct measuring fluorometry using the hematofluorometer. Because of the high sensitivity of such measurement, relatively small blood samples are required, with liquid samples or blood collected on filter paper.

The most common laboratory or wet chemical procedures now in use represent variations of several common chemical procedures: (1) treatment of blood samples with a mixture of ethyl acetate/acetic acid followed by a repartitioning into an inorganic acid medium; or (2) solubilization of a blood sample directly into a detergent/buffer solution at a high dilution. Quantification has been done using protoporphyrin, coproporphyrin, or zinc protoporphyrin IX plus pure zinc ion. The levels of precision for these laboratory techniques vary somewhat with the specifics of analysis. The Piomelli method has a coefficient of variation of 5 percent, while the direct ZPP method using buffered detergent solution is higher and more variable.

The recent development of the hematofluorometer has made it possible to carry out EP measurements in high numbers, thereby making population screening feasible. Absolute calibration is necessary and requires periodic adjustment of the system using known concentrations of EP in reference blood samples. Since these units are designed for oxygenated blood (i.e., capillary blood), use of venous blood requires an oxygenation step, usually a moderate shaking for several minutes. Measurement of low or moderate levels of EP can be affected by interference with bilirubin. Competently employed, the hematofluorometer is reasonably precise, showing a total coefficient of variation of 4.1-11.5 percent. While the comparative accuracy of the unit has been reported to be good relative to the reference wet chemical technique, a very recent study has shown that commercial units carry with them a significant negative bias, which may lead to false negatives in subjects having only moderate EP elevation. Such a bias in accuracy has been difficult to detect in existing EP proficiency testing programs. By comparison to wet methods, the hematofluorometer should be restricted to field use rather than becoming a substitute in the laboratory for chemical measurement, and this field use should involve periodic split-sample comparison testing with the wet method.

Measurement of Urinary Coproporphyrin. Although EP measurement has largely supplanted the use of urinary coproporphyrin (CP-U) analysis to monitor excessive lead exposure in humans, this measurement is still of value in that it reflects active intoxication. The standard analysis is a fluorometric technique, whereby urine samples are treated with buffer, and an oxidant (iodine) is added to generate CP from its precursor. The CP-U is then partitioned into ethyl acetate and re-extracted with dilute hydrochloric acid. The working curve is linear below 5 μg CP/dl urine.

Measurement of Delta-Aminolevulinic Acid Dehydrase Activity. Inhibition of the activity of the erythrocyte enzyme delta-aminolevulinic acid dehydrase (ALA-D) by lead is the basis for using such activity in screening for excessive lead exposure. A number of sampling and sample handling precautions attend such analysis. Since zinc (II) ion will offset the degree of activity inhibition by lead, blood collecting tubes must have extremely low zinc content, which essentially rules out the use of rubber-stoppered blood tubes. Enzyme stability is such that the activity measurement is best carried out within 24 hr of blood collection. Porphobilinogen, the product of enzyme action, is light labile and requires the assay be done in restricted light. Various procedures for ALA-D measurement are based on measurement of the level of the chromophoric pyrrole (approximately 555 nm) formed by condensation of the porphobilinogen with p-dimethylaminobenzaldehyde.

In the European Standardized Method for ALA-D activity determination, blood samples are hemolyzed with water; ALA solution is then added, followed by incubation at 37°C, and the reaction terminated by a solution of mercury (II) in trichloroacetic acid. Filtrates are treated with modified Ehrlich's reagent (p-dimethylaminobenzaldehyde) in trichloroacetic/perchloroacetic acid mixture. Activity is quantified in terms of micromoles ALA/min per liter of erythrocytes.

One variation in the above procedure is the initial use of a thiol agent, such as dithiothreotol, to reactivate the enzyme and give a measure of the full native activity of the enzyme. The ratio of activated/unactivated activity versus blood lead levels accommodates genetic differences between individuals.

Measurement of Delta-Aminolevulinic Acid in Urine and Other Media. Levels of delta-aminolevulinic acid (ALA) in urine and plasma increase with elevated lead exposure. Thus, measurement of this metabolite, generally in urine, provides an index of the level of lead exposure. ALA content of urine samples (ALA-U) is stable for about 2 weeks or more with sample acidification and refrigeration. Levels of ALA-U are adjusted for urine density or expressed per unit creatinine. If feasible, 24-hr collection is more desirable than spot sampling.

Virtually all the various procedures for ALA-U measurement employ preliminary isolation of ALA from the balance of urine constituents. In one method, further separation of ALA from the metabolite aminoacetone is done because aminoacetone can interfere with colorimetric measurement. ALA is recovered, condensed with a beta-dicarbonyl compound, e.g., acetyl acetone, to yield a pyrrole intermediate. This intermediate is then reacted with p-dimethylaminobenzaldehyde in perchloric/acetic acid, followed by colorimetric reading at 553 nm. In one variation of the basic methodology, ALA is condensed with ethyl acetoacetate directly and the resulting pyrrole extracted with ethyl acetate. Ehrlich's reagent is then added as in other procedures and the resulting chromophore is measured spectrophotometrically.

Measurement of ALA in plasma is much more difficult than in urine, since plasma ALA is at nanogram/milliter levels. In one gas-liquid chromatographic procedure, ALA is isolated from plasma, reacted with acetyl acetone and partitioned into a solvent that also serves for pyrolytic methylation of the involatile pyrrole in the injector port of the chromatograph, making the derivative more volatile. For quantification, an internal standard, 6-amino-5-oxohexanoic acid, is used. While the method is more involved, it is more specific than the older colorimetric technique.

Measurement of Pyrimidine-5'-Nucleotidase Activity. Erythrocyte pyrimidine-5'-nucleotidase (Py5N) activity is inhibited with lead exposure. Currently, two different methods are used for assaying the activity of this enzyme. The older method is quite laborious in time and effort, whereas the more recent approach is shorter and uses radioisotopes and radiometric measurement.

In the older method, heparinized venous blood is filtered through cellulose to separate erythrocytes from platelets and leukocytes. Cells are then freeze-fractured and the hemolysates dialyzed to remove nucleotides and other phosphates. This dialysate is then incubated in the presence of a nucleoside monophosphate and cofactors, the enzyme reaction being terminated by treatment with trichloroacetic acid. The inorganic phosphate isolated from added substrate is measured colorimetrically as the phosphomolybdic acid complex.

In the radiometric assay, hemolysates obtained as before are incubated with pure ^{14}C-cytidinemonophosphate. By addition of a barium hydroxide/zinc sulfate solution, proteins and unreacted nucleotide are precipitated, leaving labeled cytidine in the supernatant. Aliquots are measured for ^{14}C-activity in a liquid scintillation counter. This method shows a good correlation with the earlier technique.

Measurement of Plasma 1,25-Dihydroxyvitamin D. Measurement techniques for this vitamin D metabolite, all of recent vintage, consist of three main parts: (1) isolation from plasma or serum by liquid-liquid extraction; (2) preconcentration of the extract and chromatographic purification using Sephadex LH-20 or Lipidex 5000 columns, as well as high performance liquid chromatography (HPLC) in some cases; and (3) quantification by either of two radiometric binding techniques, the more common competitive protein binding (CPB) assay or radioimmunoassay (RIA). The CPB assay uses a receptor protein in intestinal cytosol of chicks made vitamin D-deficient.

In one typical study, human adults had a mean 1,25-dihydroxyvitamin D level of 31 picograms/ml. The limit of detection was 5 picograms/analytical tube, and within-run and between-run coefficients of variation were 17 and 26 percent, respectively. In a recent interlaboratory survey involving 15 laboratories, the level of variance was such that it was recommended that each laboratory should establish its own reference values.

1.10 METABOLISM OF LEAD

Toxicokinetic parameters of lead absorption, distribution, retention, and excretion relating external environmental lead exposure to various adverse effects are discussed in this section. Also considered are various influences on these parameters, e.g., nutritional status, age, and stage of development. A number of specific issues regarding lead metabolism by animals and humans are addressed, including the following:

1. How does the developing organism (from gestation to maturity) differ from the adult in toxicokinetic response to lead intake?
2. What do these differences in lead metabolism portend for relative risk of adverse effects?
3. What are the factors that significantly change the toxicokinetic parameters in ways relevant to assessing health risk?
4. How do the various interrelationships among body compartments of lead translate to assessment of internal exposure and changes in internal exposure?

1.10.1 Lead Absorption in Humans and Animals

There are four ways in which lead may be absorbed by the body. The amount of lead entering the bloodstream via these routes of absorption is influenced not only by the levels of the element in a given medium, but also by various physical and chemical parameters and specific host factors, such as age and nutritional status.

Respiratory Absorption of Lead. The movement of lead from ambient air to the bloodstream is a two-part process: deposition of some fraction of inhaled air lead in the deeper part of the respiratory tract and absorption of the deposited fraction. For adult humans, the deposition rate of particulate airborne lead as likely encountered by the general population is around 30-50 percent, with these rates being modified by such factors as particle size and ventilation rates. All of the lead deposited in the lower respiratory tract appears to be absorbed, so that the overall absorption rate is governed by the deposition rate, i.e., approximately 30-50 percent. Autopsy results showing no lead accumulation in the lung indicate total absorption of deposited lead.

All of the available data for lead uptake via the respiratory tract in humans have been obtained with adults. Respiratory uptake of lead in children, while not fully quantifiable, appears to be comparatively greater on a body-weight basis. A second factor influencing the relative deposition rate in children is airway dimensions; one report has estimated that the 10-year-old child has a deposition rate 1.6- to 2.7-fold higher than the adult on a weight basis.

The chemical form of the lead compound inhaled does not appear to be a major determinant of the extent of alveolar absorption of lead. While experimental animal data for quantitative assessment of lead deposition and absorption for the lung and upper respiratory tract are limited, available information from the rat, rabbit, dog, and nonhuman primate support the findings that respired lead in humans is extensively and rapidly absorbed. Over the range of air lead encountered by the general population, absorption rate does not appear to depend on air lead level.

Gastrointestinal Absorption of Lead. Gastrointestinal (GI) absorption of lead mainly involves lead uptake from food and beverages as well as lead deposited in the upper respiratory tract and eventually swallowed. It also includes ingestion of non-food material, primarily in children via normal mouthing activity and pica. Two issues of concern with lead uptake from the gut are the comparative rates of such absorption in developing versus adult organisms, including humans, and how the relative bioavailability of lead affects such uptake.

By use of metabolic balance and isotopic (radioisotope or stable isotope) studies, various laboratories have provided estimates of lead absorption in the human adult on the order of 10-15 percent. This rate can be significantly increased under fasting conditions to 45 percent, compared to lead ingested with food. The latter figure also suggests that beverage lead is absorbed to a greater degree since much beverage ingestion occurs between meals.

The relationship of the chemical/biochemical form of lead in the gut to absorption rate has been studied, although interpretation is complicated by the relatively small amounts given and the presence of various components in food already present in the gut. In general, however, chemical forms of lead and their incorporation into biological matrices seem to have a minimal impact on lead absorption in the human gut. Several studies have focused on the question of differences in GI absorption rates for lead between children and adults. Such rates for children are considerably higher than for adults: 10-15 percent for adults versus approximately 50 percent for children. Available data for the absorption of lead from nonfood items such as dust and dirt on hands are limited, but one study has estimated a figure of 30 percent. For paint chips, a value of about 17 percent has been estimated.

Experimental animal studies show that, like humans, the adult animal absorbs much less lead from the gut than the developing animal. Adult rats maintained on ordinary rat chow absorb 1 percent or less of the dietary lead. Various animal studies make it clear that the newborn absorbs a much greater amount of lead than the adult, supporting studies showing this age-dependency in humans. For example, compared to an absorption rate of about 1 percent in adult rats, the rat pup has a rate 40-50 times greater. Part, but not most, of this difference can be ascribed to a difference in dietary composition. In nonhuman primates, infant monkeys absorb 65-85 percent of lead from the gut, compared to 4 percent for the adults.

The bioavailability of lead in the GI tract as a factor in its absorption has been the focus of a number of experimental studies. These data show that: (1) lead in a number of forms is absorbed about equally, except for lead sulfide; (2) lead in dirt and dust and as different chemical forms is absorbed at about the same rate as pure lead salts added to a diet; (3) lead in paint chips undergoes significant uptake from the gut; and (4) in some cases, physical size of particulate lead can affect the rate of GI absorption. In humans, the GI absorption rate of lead appears to be independent of the quantity of lead already in the gut up to a level of at least 400 µg. In animals, dietary lead levels between 10 and 100 ppm result in reduced absorption of lead from the GI tract.

Percutaneous Absorption of Lead. Absorption of inorganic lead compounds through the skin is of much less significance than absorption through respiratory and GI routes. On the other hand, absorption through skin is far more significant than other routes of exposure for the lead alkyls (see Section 1.10.6). One recent study using human volunteers and ^{203}Pb-labeled lead acetate showed that under normal conditions, skin absorption of lead alkyls approached 0.06 percent.

Transplacental Transfer of Lead. Lead uptake by the human and animal fetus occurs readily; this uptake is apparent by the 12th week of gestation in humans and increases throughout fetal development. Cord blood contains significant amounts of lead, correlating with but somewhat lower than maternal blood lead levels. Further evidence for such transfer, besides the measured lead content of cord blood, includes fetal tissue analyses and reduction in maternal blood lead during pregnancy. There also appears to be a seasonal effect on the fetus, with summer-born children showing a trend to higher blood lead levels than those born in the spring.

1.10.2 Distribution of Lead in Humans and Animals

In this subsection, the distributional characteristics of lead in various portions of the body (blood, soft tissue, calcified tissue, and the "chelatable" or potentially toxic body burden) are discussed as a function of such variables as exposure history and age.

Lead in Blood. More than 99 percent of blood lead in humans is associated with the erythrocytes under steady-state conditions, but it is the very small fraction transported in plasma and extracellular fluid that provides lead to the various body organs. Most (~50 percent) of the erythrocyte lead is bound within the cell, primarily associated with hemoglobin (particularly HbA_2), with approximately 5 percent bound to a 10,000-dalton fraction, 20 percent to a heavier molecule, and 25 percent to lower-weight species. Several studies with lead workers and patients indicate that the fraction of lead in plasma versus whole blood increases above approximately 50-60 µg/dl blood lead.

Whole blood lead in daily equilibrium with other compartments in adult humans appears to have a biological half-life of 25-28 days and amounts to about 1.9 mg in total lead content, based on isotope studies. Other data from lead-exposed workers indicate that half-life depends on mobile lead burden. Human blood lead responds rather quickly to abrupt changes in exposure. With increased lead intake, blood lead achieves a new value in approximately 40-60 days, while a decrease in exposure may be associated with variable new blood values, depending upon the exposure history. This dependence presumably reflects lead resorption from bone. With age, furthermore, a moderate increase occurs in blood lead during adulthood. Levels of lead in blood of children tend to show a peak at 2-3 years of age (probably caused by mouthing activity), followed by a decline. In older children and adults, levels of lead are sex-related, with females showing lower levels than males even at comparable levels of exposure.

In plasma, virtually all lead is bound to albumin and only trace amounts to high-weight globulins. Which of these binding forms constitutes an "active" fraction for movement to tissues is impossible to state. The most recent studies of the erythrocyte/plasma relationship in humans indicate an equilibrium between these blood compartments, such that levels in plasma rise with levels in whole blood in fixed proportion up to approximately 50-60 µg/dl, whereupon the relationship becomes curvilinear.

Lead Levels in Tissues. Of necessity, various relationships of tissue lead to exposure and toxicity in humans must generally be obtained from autopsy samples. Limitations on these data include questions of how such samples represent lead behavior in the living population, particularly with reference to prolonged illness and disease states. The adequate characterization of exposure for victims of fatal accidents is a problem, as is the fact that such studies are cross-sectional in nature, with different age groups assumed to have had similar exposure in the past.

Soft tissues. After age 20, most soft tissues (in contrast to bone) in humans do not show age-related changes. Kidney cortex shows an increase in lead with age, which may be associated with the formation of nuclear inclusion bodies. Absence of lead accumulation in most soft tissues results from a turnover rate for lead similar to that in blood.

Based on several autopsy studies, soft-tissue lead content for individuals not occupationally exposed is generally below 0.5 µg/g wet weight, with higher values for aorta and kidney cortex. Brain tissue lead level is generally below 0.2 µg/g wet weight and shows no change with increasing age, although the cross-sectional nature of these data would make changes in low levels of brain lead difficult to discern. Autopsy data for both children and adults indicate that lead is selectively accumulated in the hippocampus, a finding that is also consistent with the regional distribution in experimental animals.

Comparisons of lead levels in soft-tissue autopsy samples from children with results from adults indicate that such values are lower in infants than in older children, while children aged 1-16 years had levels comparable to those for adult women. In one study, lead content of brain regions did not materially differ for infants and older children compared to adults. Complicating these data somewhat are changes in tissue mass with age, although such changes are less than for the skeletal system.

Subcellular distribution of lead in soft tissue is not uniform. High amounts of lead are sequestered in the mitochondria and nucleus of the cell. Nuclear accumulation is consistent with the existence of lead-containing nuclear inclusions in various species and a large body of data demonstrating the sensitivity of mitochondria to injury by lead.

Mineralizing tissue. Lead becomes localized and accumulates in human calcified tissues, i.e., bones and teeth. This accumulation in humans begins with fetal development and continues to approximately 60 years of age. The extent of lead accumulation in bone ranges up to 200 mg in men ages 60-70 years, while in women lower values have been measured. Based upon various studies, approximately 95 percent of total body lead is lodged in the bones of human adults, with uptake distributed over trabecular and compact bone. In the human adult, bone lead is both the most inert and the largest body pool, and accumulation can serve to maintain elevated blood lead levels years after exposure, particularly occupational exposure, has ended.

By comparison to human adults, only 73 percent of body lead is lodged in the bones of children, which is consistent with other information that the skeletal system of children is more metabolically active than that of adults. Furthermore, bone tissue in children is less dense than in adults. While the increase in bone lead level across childhood is modest, about two-fold if expressed as concentration, the total accumulation rate is actually 80-fold when one takes into account the 40-fold increase in skeletal mass that children undergo. To the extent that some significant fraction of total bone lead in children and adults is relatively labile, in terms of health risk for the whole organism it is more appropriate to consider the total accumulation rather than just changes in concentration.

The traditional view that the skeletal system is a "total" sink for body lead (and by implication a biological safety feature to permit significant exposure in industrialized populations) never did agree with even older information on bone physiology, e.g., bone remodelling. This view is now giving way to the idea that there are at least several bone compartments for lead, with different mobility profiles. Bone lead, then, may be more of an insidious source of long-term internal exposure than a sink for the element. This aspect of the issue is summarized more fully in the next section. Available information from studies of uranium miners and human volunteers who ingested stable isotopes indicates that there is a relatively inert bone compartment for lead, having a half-life of several decades, as well as a rather labile compartment that permits an equilibrium between bone and tissue lead.

Tooth lead also increases with age at a rate proportional to exposure and roughly proportional to blood lead in humans and experimental animals. Dentine lead is the component of teeth that is perhaps the most responsive to lead exposure since it is laid down from the time of eruption until shedding. This characteristic underlies the usefulness of dentine lead levels in assessing long-term exposure.

Chelatable lead. Mobile lead in organs and systems is potentially more active toxicologically in terms of being available to biological sites of action. Hence, this fraction of total body lead burden is a more significant predictor of imminent toxicity. In reality, direct measurement of such a fraction in human subjects would not be possible. In this regard, chelatable lead, measured as the extent of plumburesis in response to administration of a chelating agent, specifically $CaNa_2EDTA$, is now viewed as the most useful probe of undue body burden in children and adults.

A quantitative description of the inputs to the body lead fraction that is chelant-mobilizable is difficult to define fully, but it most likely includes a labile lead compartment within bone as well as within soft tissues. Support for this view includes the following: (1) the age-dependency of chelatable lead, but not lead in blood or soft tissues; (2) evidence of removal of bone lead in chelation studies with experimental animals; (3) in vitro studies of lead mobilization in bone organ explants under closely defined conditions; (4) tracer-modeling estimates in human subjects; and (5) the complex nonlinear relationship of blood lead and lead intake through various media. Data for children and adults showing a logarithmic relationship of chelatable lead to blood lead and the phenomenon of "rebound" in blood lead elevation after chelation therapy regimens (without obvious external re-exposure) offer further support.

Animal studies. Animal studies have helped to define some of the relationships of lead exposure to in vivo distribution of the element, particularly the impact of skeletal lead on whole body retention. In rats, lead administration results in an initial increase of lead levels in soft tissues, followed by loss of lead from soft tissue via excretion and transfer to bone. Lead distribution appears to be relatively independent of dose. Other studies have shown that lead loss from organs follows first-order kinetics except for loss from bone, and that the skeletal system in rats and mice is the kinetically rate-limiting step in whole-body lead clearance.

The neonatal animal seems to retain proportionally higher levels of tissue lead compared to the adult and manifests slow decay of brain lead levels while showing a significant decline over time in other tissues. This decay appears to result from enhanced lead entry to the brain because of a poorly developed brain barrier system as well as from enhanced body retention of lead by young animals.

The effects of such changes as metabolic stress and nutritional status on body redistribution of lead have been noted. Lactating mice, for example, are known to demonstrate tissue redistribution of lead, specifically bone-lead resorption with subsequent transfer of both lead and calcium from mother to pups.

1.10.3 Lead Excretion and Retention in Humans and Animals

Human Studies. Dietary lead in humans and animals that is not absorbed passes through the GI tract and is eliminated with feces, as is the fraction of air lead that is swallowed and not absorbed. Lead entering the bloodstream and not retained is excreted through the renal and GI tracts, the latter via biliary clearance. The amounts excreted through these routes are a function of such factors as species, age, and exposure characteristics.

Based upon the human metabolic balance data and isotope excretion findings of various investigators, short-term lead excretion in adult humans amounts to 50-60 percent of the absorbed fraction, with the balance moving primarily to bone and some fraction (approximately half) of this stored amount eventually being excreted. This estimated overall retention figure of 25 percent necessarily assumes that isotope clearance reflects the clearance rates for body lead in all compartments. The rapidly excreted fraction has a biological half-life of 20-25 days, similar to that for lead removal from blood, based on isotope data. This similarity indicates a steady rate of lead clearance from the body. In terms of partitioning of excreted lead between urine and bile, one study indicates that the rate of biliary clearance is about 50 percent that of renal clearance.

Lead accumulates in the human body, mainly in bone, up to around 60 years of age, when a decrease occurs with changes in intake as well as in bone mineral metabolism. As noted earlier, the total amount of lead in long-term retention can approach 200 mg (and even much higher in the case of occupational exposure). This rate corresponds to a lifetime average retention rate of 9-10 μg Pb/day. Within shorter time frames, however, retention will vary considerably because of such factors as development, disruption in the individuals' equilibrium with lead intake, and the onset of such states as osteoporosis.

The age-dependency of lead retention/excretion in humans has not been well studied, but most of the available information indicates that children, particularly infants, retain a significantly higher amount of lead than adults. While autopsy data indicate that pediatric subjects at isolated points in time actually have a lower fraction of body lead lodged in bone (which probably relates to the less dense bones of children as well as high bone mineral turnover), a full understanding of longer-term retention over childhood must consider the exponential growth rate occurring in children's skeletal systems over the time period for which bone lead concentrations have been gathered. This parameter itself represents a 40-fold mass increase. Thus, this significant skeletal growth rate has an impact on an obvious question: if children take in more lead on a body-weight basis than adults, absorb and retain more lead than adults, and show only modest elevations in blood lead compared to adults in the face of a more active skeletal system, where does the lead go? A second factor is the assumption that blood lead in children relates to body lead burden in the same quantitative fashion as in adults, an assumption that remains to be proven adequately.

Animal Studies. In rats and other experimental animals, both urinary and fecal excretion appear to be important routes of lead removal from the organism. The relative partitioning between the two modes is species- and dose-dependent. With regard to species differences, biliary clearance of lead in the dog is but 2 percent of that for the rat, while such excretion in the rabbit is 50 percent that of the rat.

Lead movement from laboratory animals to their offspring via milk constituents is a route of excretion for the mother as well as a route of exposure for the young. Comparative studies of lead retention in developing versus adult animals such as rats, mice, and nonhuman primates make it clear that retention is significantly greater in the young animal. These observations support those studies showing greater lead retention in children. Some recent data indicate that a differential retention of lead in young rats persists into the post-weaning period, calculated as either uniform dosing or uniform exposure.

1.10.4 Interactions of Lead with Essential Metals and Other Factors

The toxicological behavior of elements such as lead is affected by interactions with a variety of biochemical factors, particularly nutrients.

Human Studies. In humans, the interactive behavior of lead and various nutritional factors is expressed most significantly in young children, with such interactions occurring against a backdrop of deficiencies in a number of nutritional components. Various surveys have indicated that iron, calcium, zinc, and vitamin deficiencies are widespread among the pediatric population, particularly the poor. A number of reports have documented the association of lead absorption with suboptimal nutritional states for iron and calcium, with reduced intake being associated with increased lead absorption.

Animal Studies. Reports of lead-nutrient interactions in experimental animals have generally described such relationships for a single nutrient, using relative absorption or tissue retention in the animal to index the effect. Most of the recent data are for calcium, iron, phosphorus, and vitamin D. Many studies have established that diminished dietary calcium is associated with increased blood and soft-tissue lead content in such diverse species as the rat, pig, horse, sheep, and domestic fowl. The increased body burden of lead arises from both increased GI absorption and retention, indicating that the lead-calcium interaction operates at both the gut wall and within body compartments. Lead appears to traverse the gut via both passive and active transfer. It involves transport proteins normally operating for calcium transport, but is taken up at the site of phosphorus, not calcium, absorption.

Iron deficiency is associated with an increase of lead in tissues and increased toxicity, effects that are expressed at the level of lead uptake by the gut wall. In vitro studies indicate an interaction through receptor-binding competition at a common site, which probably involves iron-binding proteins. Similarly, dietary phosphate deficiency enhances the extent of lead retention and toxicity via increased uptake of lead at the gut wall, as both lead and phosphate are absorbed at the same site in the small intestine. Results of various studies of the resorption of phosphate along with lead have not been able to identify conclusively a mechanism for the elevation of tissue lead. Since calcium plus phosphate retards lead absorption to a greater degree than simply the sums of the interactions, an insoluble complex of all these elements may be the basis of this retardation.

Unlike the inverse relationship existing for calcium, iron, and phosphate versus lead uptake, vitamin D levels appear directly related to the rate of lead absorption from the GI tract, since the vitamin stimulates the same region of the duodenum where lead is absorbed. A number of other nutrient factors are known to have an interactive relationship with lead:

1. Increases in dietary lipids increase the extent of lead absorption, with the extent of the increase being highest with polyunsaturates and lowest with saturated fats, e.g., tristearin.
2. The interactive relationship of lead and dietary protein is not clear cut, and either suboptimal or excess protein intake will increase lead absorption.
3. Certain milk components, particularly lactose, greatly enhance lead absorption in the nursing animal.
4. Zinc deficiency promotes lead absorption, as does reduced dietary copper.

Taken collectively, human and animal data dealing with the interaction of lead and nutrients indicate that children having multiple nutrient deficiencies are in the highest exposure risk category.

1.10.5 Interrelationships of Lead Exposure with Exposure Indicators and Tissue Lead Burdens

Three issues involving lead toxicokinetics evolve toward a full connection between lead exposure and its adverse effects: (1) the temporal characteristics of internal indices of lead exposure; (2) the biological aspects of the relationship of lead in various media to various indicators in internal exposure; and (3) the relationship of various internal indicators of exposure to target tissue lead burdens.

Temporal Characteristics of Internal Indicators of Lead Exposure. The biological half-life for newly absorbed lead in blood may be as short as weeks, several months, or even longer, depending on the mobile lead burden in the body. Compared to mineral tissues, this medium reflects relatively recent exposure. If recent exposure is fairly representative of exposure over a considerable period of time, e.g., as in the case of lead workers, then blood lead is more useful than for cases where exposure is intermittent or different across time, as in the case of lead exposure of children. Accessible mineralized tissue, such as shed teeth, extend the time frame back to years of exposure, since teeth accumulate lead with age and as a function of the extent of exposure. Such measurements are, however, retrospective in nature, in that identification of excessive exposure occurs after the fact and thus limits the possibility of timely medical intervention, exposure abatement, or regulatory policy concerned with ongoing control strategies.

Perhaps the most practical solution to the dilemma posed by the different temporal characteristics of tooth and blood lead analyses is in situ measurement of lead in teeth or bone during the time when active accumulation occurs, e.g., 2- to 3-year-old children. Available data using X-ray fluorescence analysis do suggest that such approaches are feasible and can be reconciled with such issues as acceptable radiation hazard risk to subjects.

Biological Aspects of External Exposure/Internal Indicator Relationships. The literature indicates clearly that the relationship between lead in media relevant for human exposure and blood lead is curvilinear when viewed over a relatively broad range of blood lead values. This curvilinearity implies that the unit change in blood lead per unit intake of lead in some medium varies across this range of exposure, with comparatively smaller blood lead changes occurring as internal exposure increases.

Given our present knowledge, such a relationship cannot be taken to mean that body uptake of lead is proportionately lower at higher exposure, because it may simply mean that blood lead becomes an increasingly unreliable measure of target-tissue lead burden with increasing exposure. While the basis of the curvilinear relationship remains to be identified, available animal data suggest that it may be related to the increasing fraction of blood lead in plasma as blood lead increases above approximately 50-60 µg/dl.

Internal Indicator/Tissue Lead Relationships. In living human subjects, direct determination of tissue lead burdens or how these relate to adverse effects in target tissues is not possible. Some accessible indicator (e.g., measurements of lead or a biochemical surrogate of lead such as erythrocyte protoporphyrin in a medium such as blood), must be employed. While blood lead still remains the only practical measure of excessive lead exposure and health risk, evidence continues to accumulate that such an index has some limitations in either reflecting tissue lead burdens or changes in such tissues with changes in exposure.

At present, the measurement of plumburesis associated with challenge by a single dose of a lead-chelating agent such as $CaNa_2EDTA$ is considered the best indicator of the mobile, potentially toxic fraction of body lead. Chelatable lead is logarithmically related to blood lead, such that an incremental increase in blood lead is associated with an increasingly larger increment of mobilizable lead. The problems associated with this logarithmic relationship may be seen in studies of children and lead workers in whom moderate elevation in blood lead levels can disguise levels of mobile body lead. In one recent multi-institution study of 210 children, for example, 12 percent of children with blood lead 30-39 µg/dl, and 38 percent with levels of 40-49 µg/dl, had a positive EDTA-challenge response and required further evaluation or treatment. At blood lead levels such as these, the margin of protection against severe intoxication is reduced. The biological basis of the logarithmic chelatable-lead/blood-lead relationship rests, in large measure, with the existence of a sizeable bone lead compartment that is mobile enough to undergo chelation removal and, hence, potentially mobile enough to move into target tissues.

Studies of the relative mobility of chelatable lead over time indicate that, in former lead workers, removal from exposure leads to a protracted washing out of lead (from bone resorption of lead) to blood and tissues, with preservation of a bone burden amenable to subsequent chelation. Studies with children are inconclusive, since the one investigation directed to this end employed pediatric subjects who all underwent chelation therapy during periods of severe lead poisoning. Animal studies demonstrate that changes in blood lead with increasing exposure do not agree with tissue uptake in a time-concordant fashion, nor does decrease in blood lead with reduced exposure signal a similar decrease in target tissue, particularly in the brain of the developing organism.

1.10.6 Metabolism of Lead Alkyls

The lower alkyl lead components used as gasoline additives, tetraethyl lead (TEL) and tetramethyl lead (TML), may themselves pose a toxic risk to humans. In particular, there is among children a problem of sniffing leaded gasoline.

Absorption of Lead Alkyls in Humans and Animals. Human volunteers inhaling labeled TEL and TML show lung deposition rates for the lead alkyls of 37 and 51 percent, respectively, values which are similar to those for particulate inorganic lead. Significant portions of these deposited amounts were eventually absorbed. Respiratory absorption of organolead bound to particulate matter has not been specifically studied as such.

While specific data for the GI absorption of lead alkyls in humans and animals are not available, their close similarity to organotin compounds, which are quantitatively absorbed, would argue for extensive GI absorption. In contrast to inorganic lead salts, the lower lead alkyls are extensively absorbed through the skin and animal data show lethal effects with percutaneous uptake as the sole route of exposure.

Biotransformation and Tissue Distribution of Lead Alkyls. The lead alkyls TEL and TML undergo monodealkylation in the liver of mammalian species via the P-450-dependent monooxygenase enzyme system. Such transformation is very rapid. Further transformation involves conversion to the dialkyl and inorganic lead forms, the latter accounting for the effects on heme biosynthesis and erythropoiesis observed in alkyl lead intoxication. Alkyl lead is rapidly cleared from blood, and shows a higher partitioning into plasma than inorganic lead, with triethyl lead clearance being more rapid than the methyl analog.

Tissue distribution of alkyl lead in humans and animals primarily involves the trialkyl metabolites. Levels are highest in liver, followed by kidney, then brain. Of interest is the fact that there are detectable amounts of trialkyl lead from autopsy samples of human brain even in the absence of occupational exposure. In humans, there appear to be two tissue compartments for triethyl lead, having half-times of 35 and 100 days.

Excretion of Lead Alkyls. With alkyl lead exposure, excretion of lead through the renal tract is the main route of elimination. The chemical forms being excreted appear to be species-dependent. In humans, trialkyl lead in workers chronically exposed to alkyl lead is a minor component of urine lead, approximately 9 percent.

1.11 ASSESSMENT OF LEAD EXPOSURES AND ABSORPTION IN HUMAN POPULATIONS

Chapter 11 describes the effect of environmental lead exposure on human populations in terms of a change in an internal exposure index that follows changes in external exposures. The index of internal lead exposure most frequently cited is blood lead level, but other indices such as levels of lead in tooth and bone are also presented. Blood lead level estimates the body's recent exposure to environmental lead, while teeth and bone lead levels represent cumulative exposures.

Measurement of lead in blood and other physiological media has been accomplished via a succession of analytical procedures over the years. With these changes in technology there has been increasing recognition of the importance of controlling for contamination in the sampling and analytical procedures (see Section 1.9). These advances, as well as the institution of external quality control programs, have resulted in markedly improved analytic results. A generalized improvement in analytic results across many laboratories occurred during Federal Fiscal Years 1977-1979.

The main discussion in Chapter 11 is structured to achieve four main objectives:

(1) Elucidation of patterns of internal lead exposures in U.S. populations and identification of important demographic covariates.

(2) Characterization of relationships between external and internal exposures to lead by exposure medium (air, food, water, or dust).

(3) Identification of specific sources of lead which result in increased internal exposure levels.

(4) Estimation of the relative contributions of various sources of lead in the environment to total internal exposure as indexed by blood lead level.

A question of major interest in understanding environmental pollutants is the extent to which current ambient exposures exceed background levels. Ancient Nubian samples (dated 3300-2900 B.C.) averaged 0.6 μg lead/g for bone and 0.9 μg lead/g for teeth. More recent Peruvian Indian samples (12th Century) had teeth lead levels of 13.6 μg/g. Contemporary Alaskan Eskimo samples had a mean of 56.0 μg/g, while Philadelphia samples had a mean of 188.3 μg/g. These data suggest an increasing pattern of lead absorption.

Studies of current populations living in remote areas far from urbanized cultures show blood lead levels in the range of 1-5 μg/dl. In contrast to the blood lead levels found in remote populations, data from current U.S. populations have geometric means ranging from <10 to 20 μg/dl depending on age, race, sex, and degree of urbanization. These higher current exposure levels appear to be associated with industrialization and widespread commercial use of lead, e.g., as gasoline additives.

1.11.1 Levels of Lead and Demographic Covariates in U.S. Populations

The National Center for Health Statistics has provided the best currently available picture of blood lead levels among United States residents as part of the second National Health and Nutrition Examination Study (NHANES II) conducted from February, 1976 to February, 1980 (Mahaffey and Michaelson, 1980; McDowell et al., 1981; Mahaffey et al., 1982; Annest et al., 1982; Annest and Mahaffey, 1984). The national estimates are based on 9933 persons whose blood lead levels ranged from 2.0 to 66.0 μg/dl. The median blood lead for the entire U.S. population for the years of the NHANES II study (1976-1980) is 13.0 μg/dl.

Age appears to be one of the most important demographic covariates of blood lead levels, with blood lead levels in children generally higher than those in non-occupationally exposed adults; children aged 2-3 years tend to have the highest blood lead levels. The age trends in blood lead levels for children under 10 years old, as seen in three studies, are presented in

Figure 1-13. Blood lead levels in non-occupationally exposed adults may increase slightly with age due to skeletal lead accumulation.

Sex has a differential impact on blood lead levels depending on age. No significant difference exists between males and females less than seven years of age. Males above the age of seven generally have higher blood lead levels than females.

Race also plays a role, in that blacks generally have higher blood lead levels than either whites or Hispanics, and urban black children (aged 6 mo-5 yr) have markedly higher blood lead concentrations than any other racial or age group. Possible genetic factors associated with race have yet to be fully untangled from differential exposure levels and other factors as important determinants of blood lead levels.

Blood lead levels also seem to increase with degree of urbanization. Data from NHANES II show that blood lead levels in the United States, averaged from 1976 to 1980, increase from a geometric mean of 11.9 µg/dl in rural populations to 12.8 µg/dl in urban populations of less than one million and increase again to 14.0 µg/dl in urban populations of one million or more (see Table 1-9). Results obtained from the NHANES II study show that urban children generally have the highest blood lead levels of any non-occupationally exposed population group. Furthermore, black urban children have significantly higher blood lead levels than white urban children. Several case control studies of children have shown that blood lead levels are related to hand lead levels, house dust levels, lead in outside soil, interior paint lead level, and history of pica.

Knowledge of the distributional form of blood lead levels in a population is important because the distributional form determines which measure of central tendency (arithmetic mean, geometric mean, median) is most appropriate. It is even more important in estimating percentiles in the tail of the distribution, which represents those individuals at highest risk of excess exposure.

Based on examination of NHANES II data, as well as results of several other studies, it appears that the lognormal distribution is the most appropriate for describing the distribution of blood lead levels in populations thought to be homogenous in terms of demographic and lead exposure characteristics. The lognormal distribution appears to fit well across the entire range, including the upper tail of the distribution. The geometric standard deviation for four different studies are shown in Table 1-10. The values, including analytic error, are about 1.4 for children and possibly somewhat smaller for adults. This allows an estimation of the upper tail of the blood lead distribution, the group at higher risk. A somewhat larger geometric standard deviation of 1.42 maybe derived from the NHANES II study when only gasoline and industrial air lead emission exposures are assumed to be controllable sources of variation.

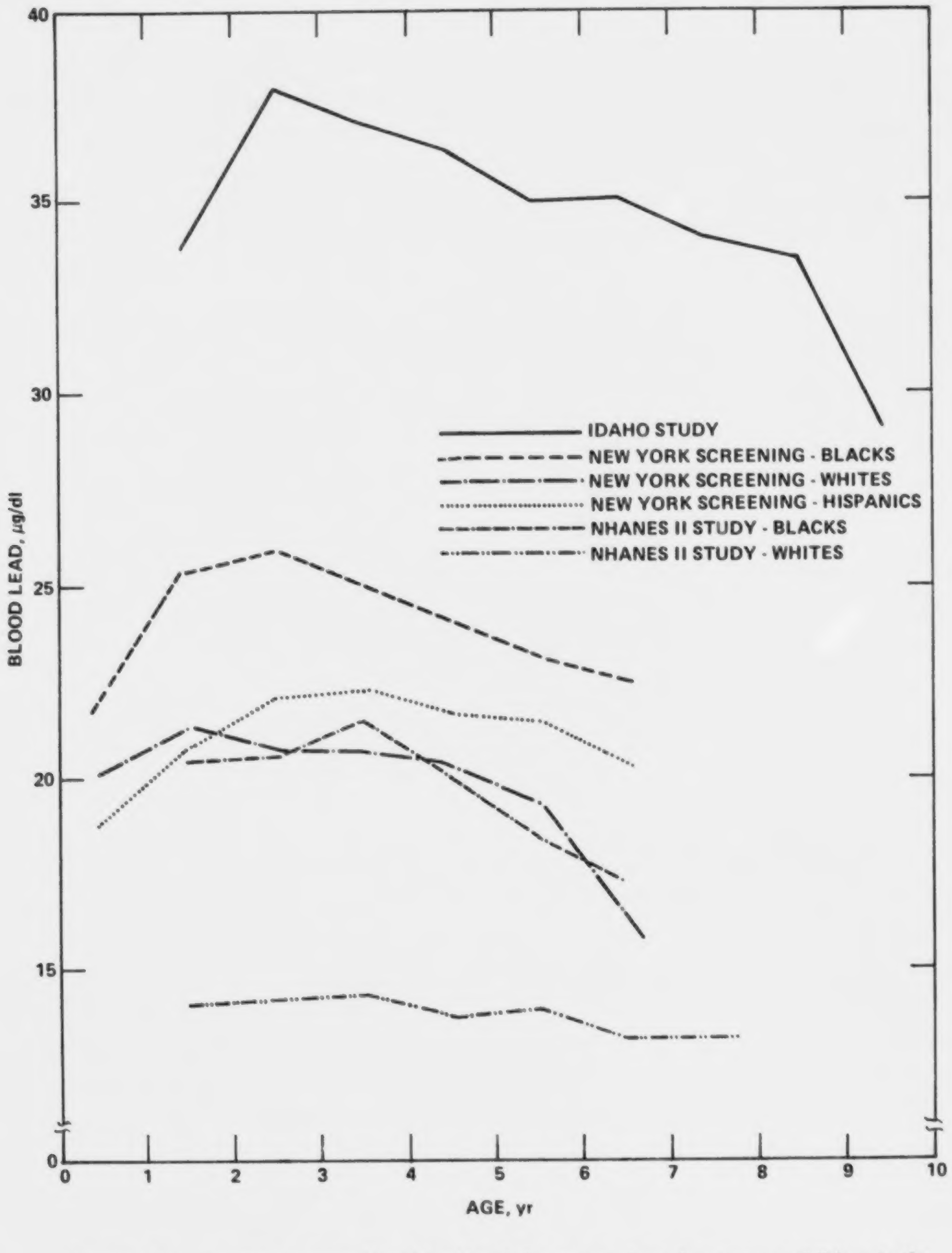

Figure 1-13. Geometric mean blood lead levels by race and age for younger children in the NHANES II Study (Annest et al., 1982), the Kellogg Silver Valley, Idaho Study (Yankel et al., 1977), and the New York Childhood Screening Studies (Billick et al., 1979).

TABLE 1-9. WEIGHTED GEOMETRIC MEAN BLOOD LEAD LEVELS FROM NHANES II SURVEY BY DEGREE OF URBANIZATION OF PLACE OF RESIDENCE IN THE UNITED STATES BY AGE AND RACE, UNITED STATES 1976-80

Race and age	Degree of urbanization Urban, ≥1 million	Urban, <1 million	Rural
All races			
All ages	14.0*	12.8	11.9
6 months-5 years	16.8	15.4	13.0
6-17 years	13.1	11.7	10.7
18-74 years - men:	16.9	15.7	15.1
women:	12.2	11.0	9.8
Whites			
All ages	14.0	12.5	11.8
6 months-5 years	15.6	14.4	12.7
6-17 years	12.6	11.4	10.5
18-74 years - men:	16.9	15.4	14.8
women:	12.4	10.8	9.8
Blacks			
All ages	14.4	14.8	14.4
6 months-5 years	20.8	19.2	16.5
6-17 years	14.6	13.6	13.0
18-74 years - men:	17.4	18.6	18.3
women:	11.8	12.4	11.3

*Values are geometric means in μg/dl.

Source: Annest and Mahaffey, 1984; Annest et al. (1982).

1.11.2 Time Trends in Blood Lead Levels Since 1970

Studies in the United States. Recent U.S. blood lead levels show that a downward trend has occurred consistently across race, age, and geographic location. The downward pattern commenced in the early part of the 1970's and has continued into 1980. This downward trend has occurred as a shift in the entire distribution and not just via a truncation in high blood lead levels. This consistency suggests a general causative factor and attempts have been made to identify the causative element; reduction of lead emitted from the combustion of leaded gasoline is a prime candidate.

TABLE 1-10. SUMMARY OF POOLED GEOMETRIC STANDARD DEVIATIONS AND ESTIMATED ANALYTIC ERRORS

	Pooled geometric standard deviations				Estimated analytic error
Study	Inner-city Black children	Inner-city White children	Adult females	Adult males	
NHANES II	1.37[a]	1.39[a]	1.36[b]	1.40[b]	0.021
N.Y. Childhood Screening Study	1.41	1.42	-	-	(c)
Tepper-Levin	-	-	1.30	-	0.056[d]
Azar et al.	-	-	-	1.29	0.042[d]

Note: To calculate an estimated person-to-person GSD, compute $\mathrm{Exp}\,[(\ln(\mathrm{GSD}))^2 - \text{Analytic Error})^{\frac{1}{2}}]$.

[a] A geometric standard deviation of 1.42 may be derived when only gasoline and industrial air lead emission exposures are assumed to be controllable sources of variability.

[b] pooled across areas of differing urbanization.

[c] not known, assumed to be similar to NHANES II.

[d] taken from Lucas (1981).

Blood lead data from the NHANES II study demonstrate well that, on a nationwide basis, there has been a significant downward trend over time (Annest et al., 1983a). Mean blood lead levels dropped from 14.6 μg/dl during the first six months of the survey to 9.2 μg/dl during the last six months. Mean values from these national data presented in six-month increments from February, 1976 to February, 1980 are displayed in Figure 1-14.

Billick and colleagues (Billick et al., 1979) have analyzed the results of blood lead screening programs conducted by the City of New York. Geometric mean blood lead levels decreased for all three racial groups and for almost all age groups in the period 1970-76.

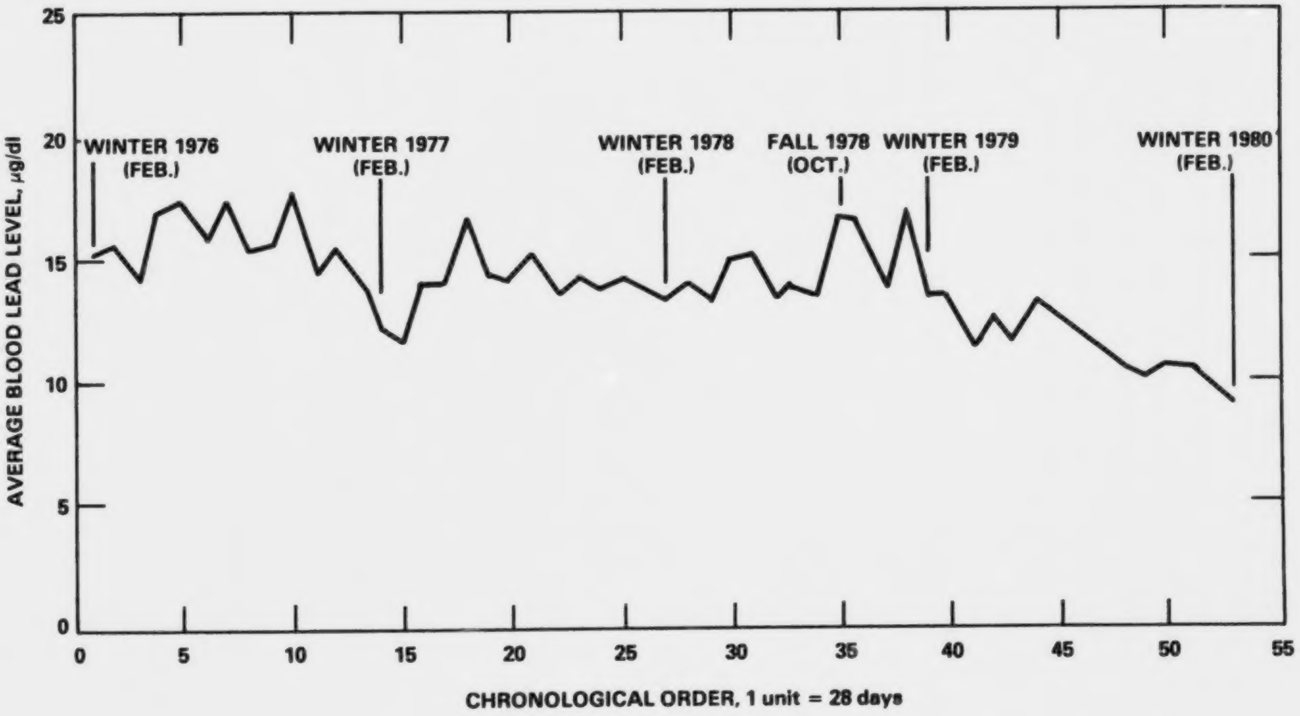

Figure 1-14. Average blood lead levels of U.S. population 6 months—74 years, United States, February 1976—February 1980, based on dates of examination of NHANES II examinees with blood lead determinations.

Source: Annest et al. (1983).

Figure 1-15 shows that the downward trend covers the entire range of the frequency distribution of blood lead levels. The decline in blood lead levels showed seasonal variability, but the decrease in time was consistent for each season.

Gause et al. (1977) present data from Newark, New Jersey, which reinforces the findings of Billick and coworkers. Gause et al. studied the levels of blood lead among 5- and 6-year-old children tested by the Newark Board of Education during the academic years 1973-74, 1974-75, and 1975-76. Blood lead levels declined markedly during this three-year period.

Rabinowitz and Needleman (1982) report a more recent study of umbilical cord blood lead levels from 11,837 births between April, 1979 and April, 1981 in the Boston area. The overall mean blood lead concentration was 6.56 ± 3.19 (standard deviation) with a range of 0.0-37.0 µg/dl. A downward trend in umbilical cord blood lead levels was noted over the two years of the study.

European Studies. There has been a series of publications from various workers in England who have been examining the question of whether or not time trends in blood lead levels exist there as well as in the United States (Oxley, 1982; Elwood, 1983a, 1983b; Quinn, 1983; Okubo et al., 1983). These papers cover a variety of exposure situations and populations. All of them obtained findings analogous to those described above for the United States, in that there has been a general decline in blood lead levels over the decade of the 1970's; they differ, however, with regard to the magnitude of the decline, when the decline began, and to what extent the decline may be attributable to a particular source of lead.

In an international study, Friberg and Vahter (1983) compared data on blood lead levels obtained in 1967 with data for 1981. For areas of the world where there were data collected by Goldwater and Hoover (1967) as well as the UN/WHO study, there was a substantial reduction in reported blood lead levels. A cautionary note must be made, however, that the analytic and human sampling procedures are not the same in the two studies. Therefore these data should be thought of as providing further, but limited, evidence supporting a recent downward trend in blood lead levels worldwide.

1.11.3 Gasoline Lead as an Important Determinant of Trends in Blood Lead Levels

Explanations have been sought for declining trends in blood lead levels observed among population groups in the United States and certain other countries since the early 1970s. Extensive evidence points towards gasoline lead as being an important determinant of changes in blood lead levels associated with exposures to airborne lead of populations in the United States and elsewhere.

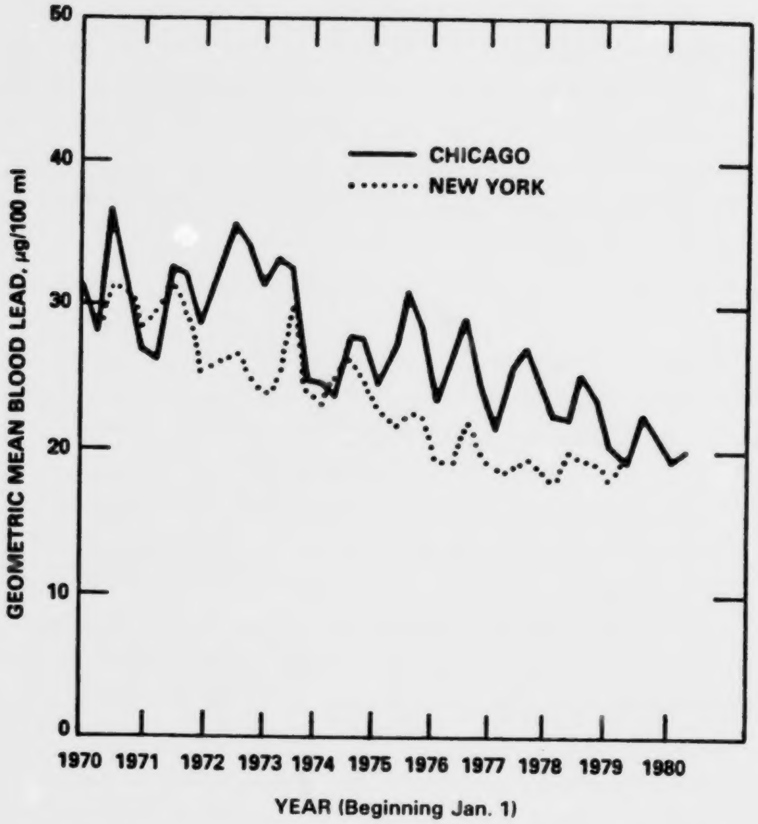

Figure 1-15. Time-dependence of blood lead for blacks, aged 24 to 35 months, in New York City and Chicago.

Source: Adapted from Billick (1982).

A striking feature of the NHANES II data was a dramatic decline in nationwide average blood lead levels in the United States during the period (1976-1980) of the survey. In evaluating possible reasons for the observed decrease in the NHANES II blood lead values, Annest (1983) and Annest et al. (1983b) found highly significant associations between the declining blood lead concentrations for the overall U.S. population and decreasing amounts of lead used in gasoline in the United States during the same time period (see Figure 1-16). The associations persisted after adjusting for race, age, sex, region of the country, season, income, and degree of urbanization (see Table 1-11). Analogous strong associations ($r = 0.95$; $p < 0.001$) were also found for blood lead levels for white children aged 6 mo-5 yr in the NHANES II sample and gasoline lead usage.

Two field investigations have attempted to derive an estimate of the amount of lead from gasoline that is absorbed by the blood of individuals. Both of these investigations used the fact that the isotopes of lead are stable; thus, the varying proportions of the isotopes present in blood and environmental samples can indicate the source of the lead. The Isotopic Lead Experiment (ILE), reported in Facchetti and Geiss (1982) and Facchetti (1985), was a massive study that attempted to utilize differing proportions of the isotopes in geologic formations to infer the proportion of lead in gasoline that is absorbed by the body. The other study (Manton, 1977; Manton, 1985) utilized existing natural shifts in isotopic proportions in an attempt to do the same thing.

The ILE was a large-scale community trial in which the geologic source of lead used in antiknock compounds in gasoline was manipulated to change the isotopic composition of lead in the atmosphere (Garibaldi et al., 1975; Facchetti, 1979). The isotopic lead ratios obtained in the samples analyzed are displayed in Figure 1-17. It can easily be seen that the airborne particulate lead rapidly changed its isotope ratio in line with expectation. Ratios in the blood samples appeared to lag somewhat behind. Background blood lead isotopic ratios were 1.1591 ± 0.0043 in rural areas and 1.1627 ± 0.0022 in Turin in 1975. In Turin school children in 1977-78, blood lead isotopic ratios tended to be somewhat lower than the ratios for Turin adults.

Preliminary analysis of the isotope ratios in air lead has allowed the estimation of the fractional contribution of gasoline lead in the city of Turin, in small communities within 25 km of Turin, and in small communities beyond 25 km (Facchetti and Geiss, 1982). At the time of maximal use of Australian lead isotope in gasoline (1978-79), about 87.3 percent of the air lead in Turin and 58.7 percent of the air lead in the countryside was attributable to gasoline. The determination of lead isotope ratios was essentially independent of specific air lead concentrations. During that time, air lead averaged about 2.0 $\mu g/m^3$ in Turin (from 0.88-4.54 $\mu g/m^3$ depending on location of the sampling site), about 0.56 $\mu g/m^3$ in the nearby communities (0.30-0.67 $\mu g/m^3$), and about 0.30 $\mu g/m^3$ in distant locations.

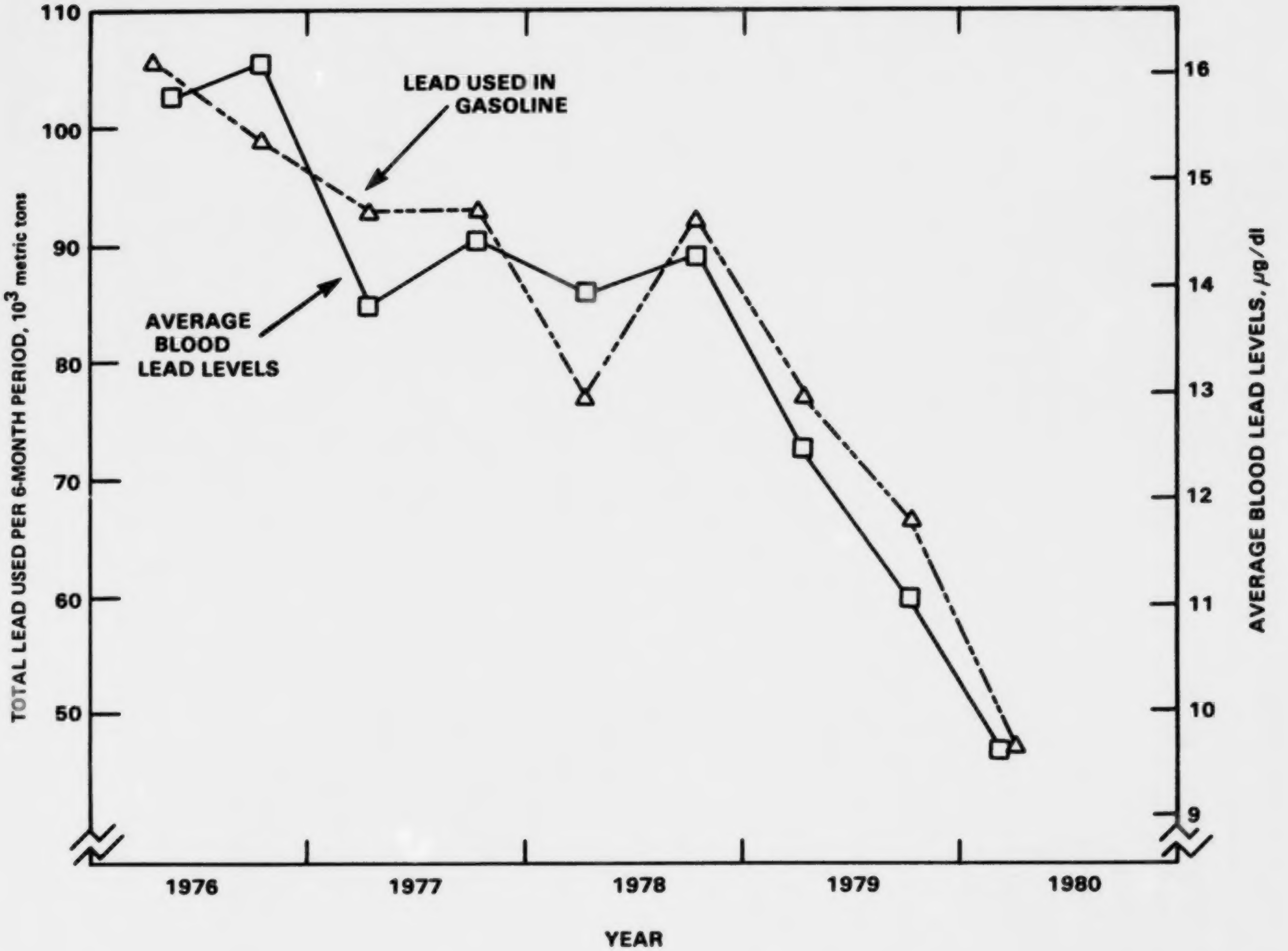

Figure 1-16. Parallel decreases in blood lead values observed in the NHANES II Study and amounts of lead used in gasoline during 1976-1980.

Source: Annest (1983).

TABLE 1-11. PEARSON CORRELATION COEFFICIENTS BETWEEN THE AVERAGE BLOOD LEAD LEVELS FOR SIX-MONTH PERIODS AND THE TOTAL LEAD USED IN GASOLINE PRODUCTION PER SIX MONTHS, ACCORDING TO RACE, SEX, AND AGE[a]

	Coefficients for 6-month Periods[b]		
	January-June and July-December[c]	April-September and October-March[d]	Averages
Overall (all races)	0.920	0.938	0.929
All black[e]	0.678	0.717	0.698
All whites	0.929	0.955	0.942
By sex: Male	0.944	0.960	0.952
Female	0.912	0.943	0.928
By age: 0.5-5 yr	0.955	0.969	0.962
6-17 yr	0.908	0.970	0.939
18-74 yr	0.920	0.924	0.922

[a] The lead values used to compute the averages were preadjusted by regression analysis to account for the effects of income, degree of urbanization, region of the country, season, and, when appropriate, race, sex, and age.

[b] All correlation coefficients were statistically significant ($p < 0.001$) except those for blacks ($p < 0.05$).

[c] Averages were based on six-month periods, except for the first and last, which covered only February 1976 through June 1976 and January 1980 through February 1980, respectively.

[d] Averages were based on six-month periods, except for the last, which covered only October 1979 through February 1980.

[e] Blacks could not be analyzed according to sex and age subgroups because of inadequate sample sizes.

Source: Annest et al. (1983b).

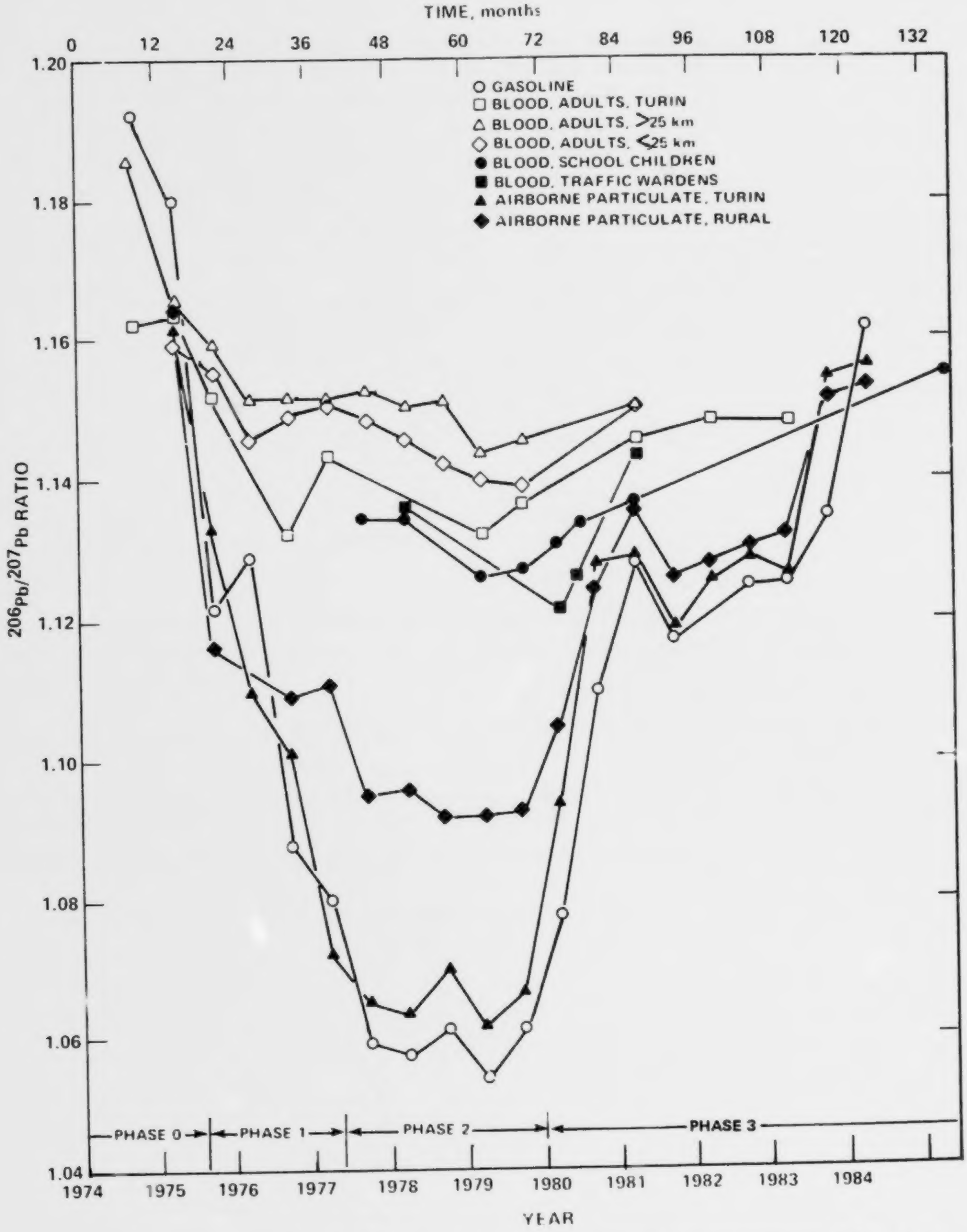

Figure 1-17. Change in ^{206}Pb/^{207}Pb ratios in gasoline, blood, and airborne particulate from 1974 to 1984.

Source: Facchetti (1985).

Isotope ratios in the blood of 63 subjects also changed, and the fraction of lead in blood attributable to gasoline could be estimated independently of blood level concentration. The mean fraction decreased from 21.4 ± 10.4 percent in Turin to 11.4 ± 7.3 percent in the nearby countryside, and to 10.1 ± 9.3 percent in the remote countryside (Facchatti, 1985).

These results can be combined with the actual blood lead concentrations to estimate the fraction of the gasoline uptake that is attributable to direct inhalation. The results are shown in Table 1-12 based upon a concept outlined in Facchetti and Geiss (1982). As concluded earlier, an assumed value of β=1.6 is plausible for predicting the amount of lead absorbed into blood at air lead concentrations less than 2.0 μg/m^3. The predicted values for airborne lead derived from leaded gasoline range from 0.28 to 2.79 μg/dl in blood due to direct inhalation. The total contribution to blood lead from gasoline lead is much larger, from 3.21-4.66 μg/dl, suggesting that the non-inhalation total contribution of gasoline increases from 1.88 μg/dl in Turin to 2.33 μg/dl in the near region and 2.93 μg/dl in the more distant region. The non-inhalation sources include ingestion of dust and soil lead and lead in food and drinking water. Efforts are being made to quantify their magnitude. The average direct inhalation of lead in the air from gasoline is 9-19 percent of the total intake attributable to gasoline in the countryside and an estimated 60 percent in the city of Turin.

The strongest kind of scientific evidence about causal relationships is based on an experiment in which all possible extraneous factors are controlled. The evidence derived from the Isotopic Lead Experiment comes very close. The experimental intervention consisted of replacing the normal ^{206}Pb/^{207}Pb isotope ratio by a very different ratio. There is no plausible mechanism by which other concurrent lead exposure variables (e.g., food, water, beverages, paint, industrial emissions) could have also changed their isotope ratios. Hence the very large changes in isotope ratios in blood were responding to the change in gasoline. There was no need to carry out detailed aerometric and ecological modeling to track the leaded gasoline isotopes through the various environmental pathways. In fact, EPA analyses* show that inhalation of community air lead will substantially underestimate the total effect of gasoline lead, at least in the 35 subjects whose blood leads were tracked in the ILE Preliminary Study. Non-inhalation sources include ingestion of dust and soil, and lead in food and drinking water. The higher water lead concentrations in the country and consumption of wine containing lead may be factors unaccounted for in the analysis. Dietary lead thus may in part explain the large excess of gasoline lead isotope ratio in blood beyond that expected from inhalation of

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*Note: The term EPA analyses refers to calculations done at EPA. A brief discussion of the methods used is contained in Appendix 11-B; more detailed information is available at EPA upon request.

TABLE 1-12. ESTIMATED CONTRIBUTION OF LEADED GASOLINE TO BLOOD LEAD BY INHALATION AND NON-INHALATION PATHWAYS

Location	Air lead fraction from gasoline[a]	Air lead conc., μg/m^3[b]	Lead fraction from gasoline[c]	Mean blood lead conc., μg/dl[d]	Blood lead from gasoline, μg/dl[e]	Lead from gasoline in air, μg/dl[f]	Non-inhaled lead from gasoline, μg/dl[g]	Estimated fraction gas-lead Inhalation[h]
Turin	0.873	2.0	0.214	21.77	4.66	2.79	1.88	0.60
<25 km	0.587	0.56	0.114	25.06	2.86	0.53	2.33	0.19
>25 km	0.587	0.30	0.101	31.78	3.21	0.28	2.93	0.09

[a] Fraction of air lead in Phase 2 attributable to lead in gasoline.

[b] Mean air lead in Phase 2.

[c] Mean fraction of blood lead in Phase 2 attributable to lead in gasoline.

[d] Mean blood lead concentration in Phase 2.

[e] Estimated blood lead from gasoline = (c) x (d)

[f] Estimated blood lead from gas inhalation = β x (a) x (b), $\beta = 1.6$.

[g] Estimated blood lead from gas, non-inhalation = (f)-(e)

[h] Fraction of blood lead uptake from gasoline attributable to direct inhalation = (f)/(e).

Data from Facchetti and Geiss (1982); Facchetti (1985).

ambient air lead; this could occur both from gasoline lead entering the food chain and being added during food processing and preparation. The subjects in the ILE study cannot be said to represent some defined population, and it is not clear how the results can be extended to U.S. populations. Turin's unusual meteorology, high blood lead levels, and the "reversed" urban-rural gradient of blood lead levels in the subjects in the ILE study indicate the need for future research. However, in spite of the variable gasoline lead exposures of the subjects, there is strong evidence that changes in gasoline lead produce large changes in blood lead.

Manton (1977) conducted a long-term study of 10 subjects whose blood lead isotopic composition was monitored for comparison with the isotopic composition of the air they breathed. Manton had observed that the ratio of ^{206}Pb/^{204}Pb in the air varied with seasons in Dallas, Texas; therefore, the ratio of those isotopes should vary in the blood. By comparing the observed variability, estimates could then be made of the amount of lead in air that is absorbed by the blood. From the Manton study, it is estimated that between 7 and 41 percent of the blood lead in study subjects in Dallas results from airborne lead. Additionally, these data provide a means of estimating the indirect contribution of air lead to blood lead. By one estimate, only 10-20 percent of the total airborne contribution to blood lead in Dallas is from direct inhalation.

Another approach to identifying the determinants of trends in blood lead levels over time was taken in New York City. Billick et al. (1979) presented several possible explanations for observed declines in blood lead levels, as well as evidence supporting and refuting each. The suggested contributing factors were the following: (1) the active educational and screening program of the New York City Bureau of Lead Poisoning Control; (2) a decrease in the amount of lead-based paint exposure as a result of rehabilitation or removal of older housing stock, and (3) changes in total environmental lead exposure. However, information was only partially available for ambient air lead levels; air lead measurements for the entire study period were available for only one station, which was located on the west side of Manhattan at a height of 56 m. Superimposition of the air lead and blood lead levels indicated a similarity in both upward cycle and decline. The authors cautioned against overinterpretation by assuming that one air monitoring site was representative of the air lead exposure of New York City residents. With this in mind, the investigators fitted a multiple regression model to the data to try to define the important determinants of blood lead levels for this population. Age, ethnic group, and air lead level were all found to be significant determinants of blood lead levels. The authors further point out the possibility of a change in the nature of the population being screened before and after 1973. They reran this regression analysis separately for years both before and after 1973. The same results were still obtained, although the exact coefficients derived varied.

Billick et al. (1980) extended their previous analysis of the data from the single monitoring site mentioned earlier and examined the possible relationship between blood lead level and the amount of lead in gasoline used in the New York City area. Figures 1-18 and 1-19 present illustrative trend lines in blood leads for blacks and Hispanics and air lead and gasoline lead, respectively. Several different measures of gasoline lead were used: (1) mid-Atlantic Coast (NY, NJ, Conn); (2) New York City plus New Jersey; and (3) New York City plus Connecticut. The lead in gasoline trend line appears to fit the blood lead trend line better than the air lead trend, especially in the summer of 1973.

1.11.4 Blood Lead versus Inhaled Air Lead Relationships

The mass of data on the relationship of blood lead level and air lead exposure is complicated by the need for reconciling the results of experimental and observational studies. Further, the process of determining the best form of the statistical relationship deduced is problematic due to the lack of consistency in the range of the air lead exposures encountered in the various studies.

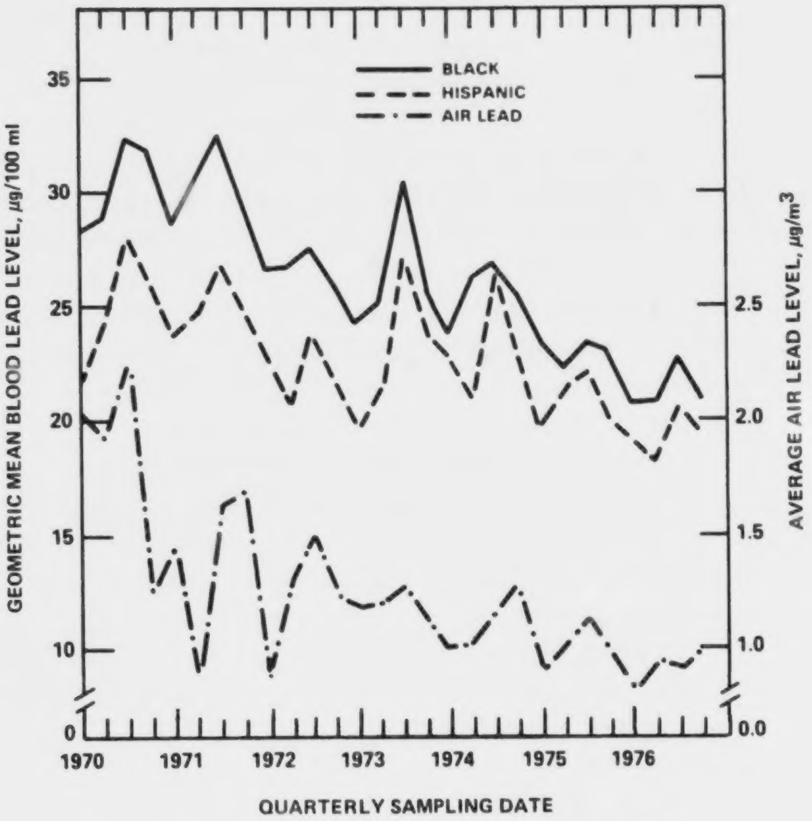

Figure 1-18. Geometric mean blood lead levels of New York City children (aged 25-36 months) by ethnic group, and ambient air lead concentrations versus quarterly sampling period, 1970-1976.

Source: Billick et al. (1980).

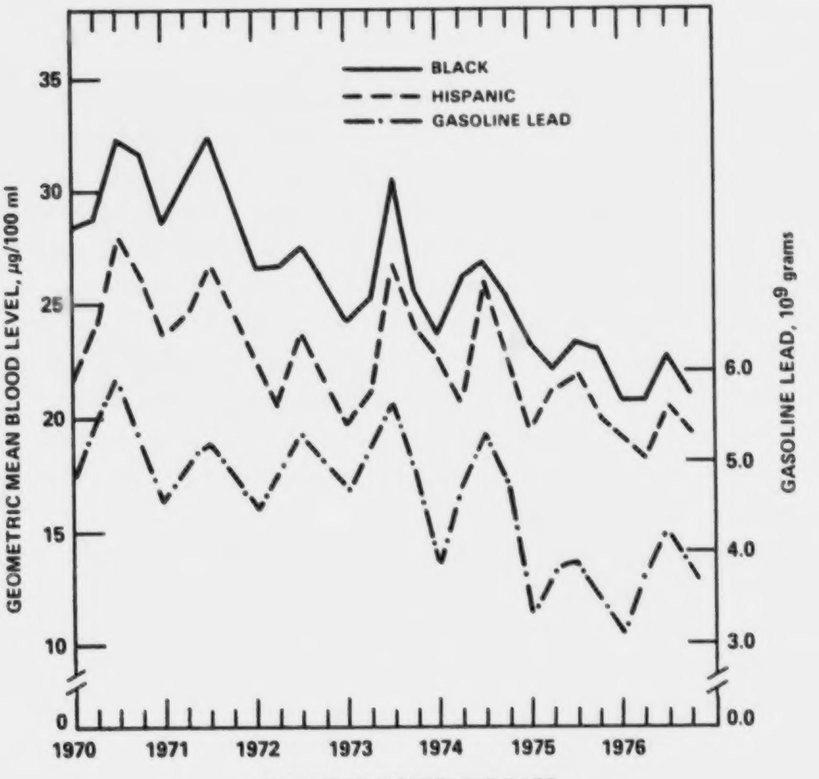

Figure 1-19. Geometric mean blood lead levels of New York City children (aged 25-36 months) by ethnic group, and estimated amount of lead present in gasoline sold in New York, New Jersey, and Connecticut versus quarterly sampling period, 1970-1976.

Source: Billick et al. (1980).

The model used is especially critical in situations where lead is present in relatively low concentrations in one or more environmental media. A large number of statistical models have been used to predict the contribution to blood lead level from various environmental media. There is no question that the relationship between blood lead and environmental exposure is nonlinear across the entire range of potential exposures, from very low to high levels. At lower levels of exposure, however, various models all provide adequate descriptions of the observed data. The choice of a model must be based at least in part on the biological mechanisms; at the very least, no model should be adopted which is inconsistent with biological reality.

Because the main purpose of this document is to examine relationships between lead in air and lead in blood under ambient conditions, EPA has chosen to emphasize the results of studies most appropriately addressing this issue. A summary of the most appropriate studies appears in Table 1-13. At air lead exposures of 3 µg/m^3 or less, there is no statistically significant difference between curvilinear and linear blood lead-inhalation relationships. At air lead exposures of 10 µg/m^3 or more, either nonlinear or linear relationships can be fitted. Thus, a reasonably consistent picture emerges in which the blood lead-air lead relationship for direct inhalation is approximately linear in the range of normal ambient exposures (0.1 - 2.0 µg/m^3.) Therefore EPA has fitted linear relationships to blood lead levels in the studies to be described with the explicit understanding that the fitted relationships are intended only to describe changes in blood due to modest changes in air lead among individuals whose blood lead levels do not exceed 30 µg/dl.

The blood lead inhalation slope estimates vary appreciably from one subject to another in experimental and clinical studies, and from one study to another. The weighted slope and standard error estimates from the Griffin et al. (1975) study (1.75 ± 0.35) were combined with those calculated similarly for the Rabinowitz et al. (1973, 1976, 1977) study (2.14 ± 0.47) and the Kehoe (1961a,b,c) study (1.25 ± 0.35, setting DH = 0), yielding a pooled weighted slope estimate of 1.64 ± 0.22 µg/dl per µg/m^3. There are some advantages in using these experimental studies on adult males, but certain deficiencies are acknowledged. The Kehoe study exposed subjects to a wide range of lead levels while in the exposure chamber, but did not control air lead exposures outside the chamber. The Griffin study provided reasonable control of air lead exposure during the experiment, but difficulties in defining the non-inhalation baseline for blood lead (especially in the important experiment at 3 µg/m^3) add much uncertainty to the estimate. The Rabinowitz study controlled well for diet and other factors and, since stable lead isotope tracers were used, there was no baseline problem. However, the actual air lead exposure of these subjects outside the metabolic ward was not well determined.

TABLE 1-13. SUMMARY OF BLOOD INHALATION SLOPES (β) (μg/dl per μg/m³)

Population	Study	Study type	N	Slope	Model sensitivity[a] of slope
Children	Angle and McIntire (1979) Omaha, NE	Population	1074	1.92	(1.40-4.40)[b,c,d]
	Roels et al. (1980) Belgium	Population	148	2.46	(1.55-2.46)[b,c]
	Yankel et al. (1977); Walter et al. (1980) Idaho	Population	879	1.52	(1.07-1.52)[b,c,d]
Adult Male	Azar et al. (1975). Five groups	Population	149	1.32	(1.08-1.59)[c,d]
	Griffin et al. (1975) NY prisoners	Experiment	43	1.75	(1.52-3.38)[e]
	Gross (1979)	Experiment	6	1.25	(1.25-1.55)[c]
	Rabinowitz et al. (1973, 1976, 1977)	Experiment	5	2.14	(2.14-3.51)[f]

[a] Selected from among the most plausible statistically equivalent models. For nonlinear models, slope at 1.0 μg/m³.

[b] Sensitive to choice of other correlated predictors such as dust and soil lead.

[c] Sensitive to linear versus nonlinear at low air lead.

[d] Sensitive to age as a covariate.

[e] Sensitive to baseline changes in controls.

[f] Sensitive to assumed air lead exposure.

Among population studies, only the Azar study provides a slope estimate in which individual air lead exposures are known. However, there was no control of dietary lead intake or other factors that affect blood lead levels, and slope estimates assuming only air lead and location as covariables (1.32 ± 0.38) are not significantly different from the pooled experimental studies.

There are no experimental inhalation studies on adult females or on children. The inhalation slope for women should be roughly the same as that for men, assuming proportionally smaller air intake and blood volume. The assumption of proportional size is less plausible for children. Slope estimates for children from population studies are used in which some other important covariates of lead absorption were controlled or measured, e.g., age, sex, dust exposure in the environment or on the hands. Inhalation slopes were estimated for the studies of Angle and McIntire (1979) [1.92 ± 0.60], Roels et al. (1980) [2.46 ± 0.58], and Yankel et al. (1977) [1.53 ± 0.064)]. The standard error of the Yankel study is extremely low and a weighted pooled slope estimate for children would reflect essentially that study alone; in this case the small standard error estimate is attributable to the very large range of air lead exposures of children in the Silver Valley (up to 22 µg/m^3). The relationship is in fact not linear, but increases more rapidly in the upper range of air lead exposures, and the slope estimate at lower air lead concentrations may not wholly reflect uncertainty about the shape of the curve at higher concentrations. The median slope of the three studies is 1.92 µg/dl per µg/m^3.

Chapter 11 evaluates the effects of atmospheric lead on blood lead in a disaggregate manner broken down according to exposure media, including direct inhalation of atmospheric lead, ingestion of particulate lead that has fallen out as dust and surface soil, and air lead ingested in consuming food and beverages (including lead absorbed from soil and added during processing and preparation). Disaggregate analyses based on various pathways for environmental lead of the type presented appear to provide a sensitive tool for predicting blood lead burdens under changes of environmental exposure. However, some authors, e.g., Brunekreef (1984) make a strong argument for the use of air lead as the single exposure criterion. Their argument is that exposure to air lead is usually of sufficient duration that the contributions along other pathways have stabilized and are proportional to the air lead concentration. In that case, the ratio between blood lead and air lead plus dust, food, and other proportional increments must be much larger than for air lead by direct inhalation alone.

The range of β values that Brunekreef (1984) reports is very large, and typical values of 3-5 are larger than those adjusted slopes (1.52-2.46) derived by EPA in preceding sections. If the aggregate approach is accepted, then the blood lead versus total (both direct and indirect) air lead slope for children may be approximately double the slope (~2.0) estimated for the direct contribution due to inhaled air lead alone.

The following statements summarize the situation briefly: (1) The experimental studies at lower air lead levels (3.2 μg/m^3 or less) and lower blood levels (typically 30 μg/dl or less) have linear blood lead inhalation relationships with slopes β_i of 0-3.6 for most subjects. A typical value of 1.64 ± 0.22 may be assumed for adults; (2) Population cross-sectional studies at lower air lead and blood lead levels are approximately linear with slopes β of 0.8-2.0; (3) Cross-sectional studies in occupational exposure situations in which air lead levels are higher (much above 10 μg/m^3) and blood lead levels are higher (above 40 μg/dl) show a much more shallow linear blood lead inhalation relation. The slope β is in the range of 0.03-0.2; (4) Cross-sectional and experimental studies at levels of air lead somewhat above the higher ambient exposures (9-36 μg/m^3) and blood leads of 30-40 μg/dl can be described either by a nonlinear relationship with decreasing slope or by a linear relationship with intermediate slope, approximately $\beta = 0.5$. Several biological mechanisms for these differences have been discussed (Hammond et al., 1981; O'Flaherty et al., 1982; Chamberlain, 1983; Chamberlain and Heard, 1981). Since no explanation for the decrease in steepness of the blood lead inhalation response to higher air lead levels has been generally accepted at this time, there is little basis on which to select a formula for interpolating from low air lead to high air lead exposures. The increased steepness of the inhalation curve for the Kellogg/Silver Valley study is inconsistent with the other studies presented. It may be that smelter situations are unique and must be analyzed differently, or it may be that the curvatuve is the result of imprecise exposure estimates; (5) The blood-lead inhalation slope for children is at least as steep as that for adults, with a median estimate of 1.92 from three major studies. These slope estimates are based on the assumption that an equilibrium level of blood lead is achieved within a few months after exposure begins. This is only approximately true, since lead stored in the skeleton may return to blood after some years. Chamberlain et al. (1978) suggest that long-term inhalation slopes should be about 30 percent larger than these estimates. Inhalation slopes quoted here are associated with a half-life of blood lead in adults of about 30 days. O'Flaherty et al. (1982) suggest that the blood lead half-life may increase slightly with duration of exposure, but this has not been confirmed (Kang et al., 1983). (6) Slopes which include both direct (inhalation) and indirect (via soil, dust, etc.) air lead contributions are necessarily higher than those estimates for inhaled air lead alone. Studies using aggregate analyses (direct and indirect air impacts) typically yield slope values in the range of 3-5, about double the slope due to inhaled air lead alone. [Other studies, reviews, and analyses of the study are discussed in Section 11.4, to which the reader is referred for a detailed discussion and for a review of the key studies and their analyses.]

It must not be assumed that the direct inhalation of air lead is the only air lead contribution that needs to be considered. Smelter studies allow partial assessment of the air lead contributions to soil, dust, and finger lead. Useful ecological models to study the possible propagation of lead through the food chain have not yet been developed. The direct inhalation relationship does provide useful information on changes in blood lead as responses to changes in air lead on a time scale of several months. The indirect pathways through dust, soil, and the food chain may thus delay the total blood lead response to changes in air lead, perhaps by one or more years.

1.11.5 Studies Relating Dietary Lead Exposures (Including Water) to Blood Lead

Dietary absorption of lead varies greatly from one person to another and depends on the physical and chemical form of the carrier, on nutritional status, and on whether lead is ingested with food or between meals. These distinctions are particularly important for consumption of leaded paint, dust, and soil by children. Typical values of 10 percent absorption of ingested lead into blood have been assumed for adults and 25-50 percent for children.

It is difficult to obtain accurate dose-response relationships between blood lead levels and lead levels in food or water. Dietary intake must be estimated by duplicate diets or fecal lead determinations. Water lead levels can be determined with some accuracy, but the varying amounts of water consumed by different individuals adds to the uncertainty of the estimated relationships.

Quantitative analyses relating blood lead levels and dietary lead exposures have been reported and studies on infants provide estimates that are in close agreement. While only one individual study has been done on adults, another estimate from a number of pooled studies is also available; these two estimates are in good agreement. Most of the subjects in the Sherlock et al. (1982) and United Kingdom Central Directorate on Environmental Pollution (1982) studies received quite high lead levels in their diets (>300 µg/day). Although the fitted cube root equations give high slopes at lower dietary lead levels, the linear slope of the United Kingdom Central Directorate on Environmental Pollution (1982) study is probably an underestimate of the slope at lower dietary lead levels. Most of the dietary intake supplements used in these two studies were so high that many of the subjects had blood lead concentrations much in excess of 30 µg/dl for a considerable part of the experiment. Blood lead levels thus may not completely reflect lead exposure, due to the previously noted nonlinearity of blood lead response at high exposures. For these reasons, the Ryu et al. (1983) study is the most believable, although it only applies to infants and also probably underestimates to some extent the value of the slope.

The slope estimates for adult dietary lead intake are an approximately 0.02 µg/dl increase in blood lead per µg/day intake, but consideration of blood lead kinetics may increase this value to about 0.04 µg/dl per µg/day intake. Such values are somewhat lower (about 0.05 µg/dl per µg/day) than those estimated from population studies extrapolated to typical dietary intakes; the value estimated for infants is much larger (0.16). Estimates for adults should be taken from the experimental studies or calculated from assumed absorption and half-life values.

The relationship between blood lead and water lead is not clearly defined and is often described as nonlinear. Water lead intake varies greatly from one person to another. It has been assumed that children can absorb 25-50 percent of lead in water. Many authors chose to fit cube root models to their data, although polynomial and logarithmic models were also used. Unfortunately, the form of the model greatly influences the estimated contributions to blood lead levels from relatively low water lead concentrations.

Although there is close agreement in quantitative analyses of relationships between blood lead levels and dietary lead concentrations, there is a larger degree of variability in results of the various water lead studies. The relationship is curvilinear but its exact form is yet to be determined. At typical water lead levels for U.S. populations, the relationship appears to be linear. The only study that determines the relationship based on lower water lead values (<100 µg/l) is the Pocock et al. (1983) study. The data from this study, as well as the authors themselves, suggest that the relationship is linear for this lower range of water lead levels. Furthermore, the estimated contributions to blood lead levels from this study are quite consistent with the polynomial models from other studies. For these reasons, the Pocock et al. (1983) slope of 0.06 is considered to represent the best estimate. The possibility still exists, however, that the higher estimates of the other studies may be correct in certain situations, especially at higher water lead levels (>100 µg/l).

1.11.6 Studies Relating Lead in Soil and Dust to Blood Lead

The relationship of exposure to lead contained in soil and house dust and the amount of lead absorbed by humans, particularly children, has been the subject of a number of scientific investigations. Some of these studies have been concerned with the effects of exposures resulting from the ingestion of lead in dust (Duggan and Williams, 1977; Barltrop, 1975; Creason et al., 1975); others have concentrated on the means by which the lead in soil and dust becomes available to the body (Sayre et al., 1974). Sayre et al. (1974) demonstrated the feasibility of house dust as a source of lead for children in Rochester, NY. Two groups of houses, one inner city and the other suburban, were chosen for the study. Lead-free sanitary paper towels were used to collect dust samples from house surfaces and the hands of children (Vostal et al., 1974). The medians for the hand and household samples were used as the cut-points in the chi-square contingency analysis. A statistically significant difference between the urban and suburban homes for dust levels was noted, as was a relationship between household dust levels and hand dust levels (Lepow et al., 1975).

Studies relating soil lead to blood lead levels are difficult to compare. The relationship obviously depends on depth of soil lead, age of the children, sampling method, cleanliness of the home, mouthing activities of the children, and possibly many other factors. Various soil sampling methods and sampling depths have been used over time; as such they may not be directly comparable and may produce a dilution effect of the major lead concentration contribution from dust, which is located primarily in the top 2 cm of the soil.

Increases in soil lead significantly increase blood lead in children. From several studies, EPA estimates an increase of 0.6-6.8 µg/dl in blood lead for each increase of 1000 µg/g in soil lead concentration. This range is similar to the range of 1.0 to 10.0 reported by Duggan (1980, 1983). Two studies providing good data for slope estimates are the Stark et al. (1982) study and the Angle and McIntire (1982) study. These two studies gave slope estimates of 2.2 and 6.8 µg/dl per 1000 µg/g, respectively.

The relationship of house dust lead to blood lead is even more difficult to obtain. Three studies have data permitting such calculations. The median value of 1.8 µg/dl per 1000 µg/g for children 2-3 years old in the Stark study may also represent a reasonable value for use here.

1.11.7 Additional Exposures

A major source of environmental lead exposure for many members of the general population comes from lead contained in both interior and exterior paint on dwellings. The amount of lead present, as well as its accessibility, depends upon the age of the residence (because older buildings contain paint manufactured before lead content was regulated) and the physical condition of the paint. In a survey of lead levels in 2370 randomly selected dwellings in Pittsburgh, PA (Shier and Hall, 1977), paints with high levels of lead were most frequently found in pre-1940 residences. One cannot assume, however, that high-level leaded paint is absent in dwellings built after 1940. In the case of the houses surveyed in Pittsburgh, about 20 percent of the residences built after 1960 have at least one surface with more than 1.5 mg/cm^2 lead. In fiscal year 1981, the U.S. Centers for Disease Control (1982) screened 535,730 children and found 21,897 with lead toxicity. Of these cases, 15,472 dwellings were inspected and 10,666 (approximately 67 percent) were found to have leaded paint.

A number of specific environmental sources of airborne lead have been identified as having a direct influence on blood lead levels. Primary lead smelters, secondary lead smelters, and battery plants emit lead directly into the air and ultimately increase soil and dust lead concentrations in their vicinity. Adults, and especially children, have been shown to exhibit elevated blood lead levels when living close to these sources. Blood lead levels in these residents have been shown to be related to air, as well as to soil or dust exposures.

The habit of cigarette smoking is a source of lead exposure. Other sources include the following: lead based cosmetics, lead-based folk remedies, and glazed pottery.

1.12 BIOLOGICAL EFFECTS OF LEAD EXPOSURE

1.12.1 Introduction

Lead has diverse biological effects in humans and animals. Its effects are seen at the subcellular level of organellar structures and processes as well as at the overall level of general functioning that encompasses all systems of the body operating in a coordinated, interdependent fashion.

This review not only seeks to categorize and describe the various biological effects of lead, but also attempts to identify the exposure levels at which such effects occur and the mechanisms underlying them. The dose-response curve for the entire range of biological effects exerted by lead is rather broad, with certain biochemical changes occurring at relatively low levels of exposure and perturbations in other systems, such as the liver, becoming detectable only at relatively high exposure levels. In terms of relative vulnerability to deleterious effects of lead, the developing organism generally appears to be more sensitive than the mature individual.

It should be noted that lead has no known beneficial biological effects. Available evidence does not demonstrate that lead is an essential element.

1.12.2 Subcellular Effects of Lead

The biological basis of lead toxicity is its ability to bind to ligating groups in biomolecular substances crucial to various physiological functions, thereby interfering with these functions by, for example, competing with native essential metals for binding sites, inhibiting enzyme activity, or inhibiting or otherwise altering essential ion transport. These effects are modulated by: 1) the inherent stability of such binding sites for lead; 2) the compartmentalization kinetics governing lead distribution among body compartments, among tissues, and within cells; and 3) the differences in biochemical organization across cells and tissues due to their specific functions. Given the complexities introduced by items 2 and 3, it is not surprising that no single unifying mechanism of lead toxicity across all tissues in humans and experimental animals has yet been demonstrated.

Insofar as the effects of lead on the activity of various enzymes are concerned, many of the available studies examined the *in vitro* behavior of relatively pure enzymes and have only marginal relevance to various effects *in vivo*. On the other hand, certain enzymes are basic to the effects of lead at the organ or organ system level, and discussion is best reserved for such effects in the summary sections below which deal with lead's effects on particular organ systems. This section is mainly concerned with organellar effects of lead, especially those which provide some rationale for lead toxicity at higher levels of biological organization. Particular emphasis is placed on the mitochondrion, because this organelle is not only affected by lead in numerous ways but has also provided the most data bearing on the subcellular effects of lead.

The critical target organelle for lead toxicity in a variety of cell and tissue types clearly is the mitochondrion, followed probably by cellular and intracellular membranes. The mitochondrial effects take the form of structural changes and marked disturbances in mitochondrial function within the cell, particularly in energy metabolism and ion transport. These effects in turn are associated with demonstrable accumulation of lead in mitochondria, both *in vivo* and *in vitro*. Structural changes include mitochondrial swelling in a variety of cell types, as well as distortion and loss of cristae, which occur at relatively moderate lead levels. Similar changes have also been documented in lead workers across a range of exposures.

Uncoupled energy metabolism, inhibited cellular respiration using both succinate and nicotinamide adenine dinucleotide (NAD)-linked substrates, and altered kinetics of intracellular calcium have been demonstrated *in vivo* using mitochondria of both brain and non-neural tissues. In some cases, the lead exposure level associated with such changes has been relatively low. Several studies document the relatively greater sensitivity of this organelle in young versus adult animals in terms of mitochondrial respiration. The cerebellum appears to be particularly sensitive, providing a connection between mitochondrial impairment and lead encephalopathy. Lead's impairment of mitochondrial function in the developing brain has also been consistently associated with delayed brain development, as indexed by content of various cytochromes. In the rat pup, ongoing lead exposure from birth is required for this effect to be expressed, indicating that such exposure must occur before, and is inhibitory to, the burst of oxidative metabolic activity that occurs in the young rat at 10-21 days postnatally.

In vivo lead exposure of adult rats also markedly inhibits calcium turnover in a cellular compartment of the cerebral cortex that appears to be the mitochondrion. This effect has been seen at a brain lead level of 0.4 µg/g. These results are consistent with a separate study showing increased retention of calcium in the brain of lead-dosed guinea pigs. Numerous reports have described the *in vivo* accumulation of lead in mitochondria of kidney, liver, spleen, and brain tissue, with one study showing that such uptake was slightly more than that which occurred in the cell nucleus. These data are not only consistent with deleterious effects of lead on mitochondria, but are also supported by other investigations *in vitro*.

Significant decreases in mitochondrial respiration in vitro using both NAD-linked and succinate substrates have been observed for brain and non-neural tissue mitochondria in the presence of lead at micromolar levels. There appears to be substrate specificity in the inhibition of respiration across different tissues, which may be a factor in differential organ toxicity. Also, a number of enzymes involved in intermediary metabolism in isolated mitochondria have been observed to undergo significant inhibition of activity with lead.

Of particular interest regarding lead's effects on isolated mitochondria are ion transport effects, especially in regard to calcium. Lead movement into brain and other tissue mitochondria involves active transport, as does calcium. Recent sophisticated kinetic analyses of desaturation curves for radiolabeled lead or calcium indicate that there is striking overlap in the cellular metabolism of calcium and lead. These studies not only establish the basis for the easy entry of lead into cells and cell compartments, but also provide a basis for lead's impairment of intracellular ion transport, particularly in neural cell mitochondria, where the capacity for calcium transport is 20-fold higher than even in heart mitochondria.

Lead is also selectively taken up in isolated mitochondria in vitro, including the mitochondria of synaptosomes and brain capillaries. Given the diverse and extensive evidence of lead's impairment of mitochondrial structure and function as viewed from a subcellular level, it is not surprising that these derangements are logically held to be the basis of dysfunction of heme biosynthesis, erythropoiesis, and the central nervous system. Several key enzymes in the heme biosynthetic pathway are intramitochondrial, particularly ferrochelatase. Hence, it is to be expected that entry of lead into mitochondria will impair overall heme biosynthesis, and, in fact, this appears to be the case in the developing cerebellum. Furthermore, relatively moderate levels of lead may be associated with its entry into mitochondria and consequent expressions of mitochondrial injury.

Lead exposure provokes a typical cellular reaction in humans and other species that has been morphologically characterized as a lead-containing nuclear inclusion body. While it has been postulated that such inclusions constitute a cellular protection mechanism, such a mechanism is an imperfect one. Other organelles, e.g., the mitochondrion, also take up lead and sustain injury in the presence of nuclear inclusion formations.

In theory, the cell membrane is the first organelle to encounter lead and it is not surprising that cellular effects of lead can be ascribed to interactions at cellular and intracellular membranes in the form of disturbed ion transport. The inhibition of membrane (Na^+,K^+)-ATPase of erythrocytes as a factor in lead-impaired erythropoiesis is noted in Section 1.12.3. Lead also appears to interfere with the normal processes of calcium transport across membranes of different tissues. In peripheral cholinergic synaptosomes, lead is associated with retarded release of acetylcholine owing to a blockade of calcium binding to the membrane, while calcium accumulation within nerve endings can be ascribed to inhibition of membrane (Na^+,K^+)-ATPase.

Lysosomes accumulate in renal proximal convoluted tubule cells of rats and rabbits given lead over a range of dosing. This also appears to occur in the kidneys of lead workers and seems to represent a disturbance in normal lysosomal function, with the accumulation of lysosomes being due to enhanced degradation of proteins because of the effects of lead elsewhere within the cell.

1.12.3 Effects of Lead on Heme Biosynthesis, Erythropoiesis, and Erythrocyte Physiology in Humans and Animals

The effects of lead on heme biosynthesis are well known because of their clinical prominence and the numerous studies of such effects in humans and experimental animals. The process of heme biosynthesis starts with glycine and succinyl-coenzyme A, proceeds through formation of protoporphyrin IX, and culminates with the insertion of divalent iron into the porphyrin ring to form heme. In addition to being a constituent of hemoglobin, heme is the prosthetic group of many tissue hemoproteins having variable functions, such as myoglobin, the P-450 component of the mixed-function oxygenase system, and the cytochromes of cellular energetics. Hence, disturbance of heme biosynthesis by lead poses the potential for multiple-organ toxicity.

In investigations of lead's effects on the heme synthesis pathway (Figure 1-20), most attention has been devoted to the following: (1) stimulation of mitochondrial delta-aminolevulinic acid synthetase (ALA-S), which mediates formation of delta-aminolevulinic acid (ALA); (2) direct inhibition of the cytosolic enzyme, delta-aminolevulinic acid dehydrase (ALA-D), which catalyzes formation of porphobilinogen from two units of ALA; and (3) inhibition of insertion of iron (II) into protoporphyrin IX to form heme, a process mediated by ferrochelatase.

Increased ALA-S activity has been found in lead workers as well as in lead-exposed animals, although an actual decrease in enzyme activity has also been observed in several experimental studies using different exposure methods. It appears, then, that the effect on ALA-S activity may depend on the nature of the exposure. Using rat liver cells in culture, ALA-S activity was stimulated *in vitro* at levels as low as 5.0 µM or 1.0 µg Pb/g preparation. The increased activity was due to biosynthesis of more enzyme. The blood lead threshold for stimulation of ALA-S activity in humans, based on a study using leukocytes from lead workers, appears to be about 40 µg/dl. Whether this apparent threshold applies to other tissues depends on how well the sensitivity of leukocyte mitochondria mirrors that in other systems. The relative impact of ALA-S activity stimulation on ALA accumulation at lower lead exposure

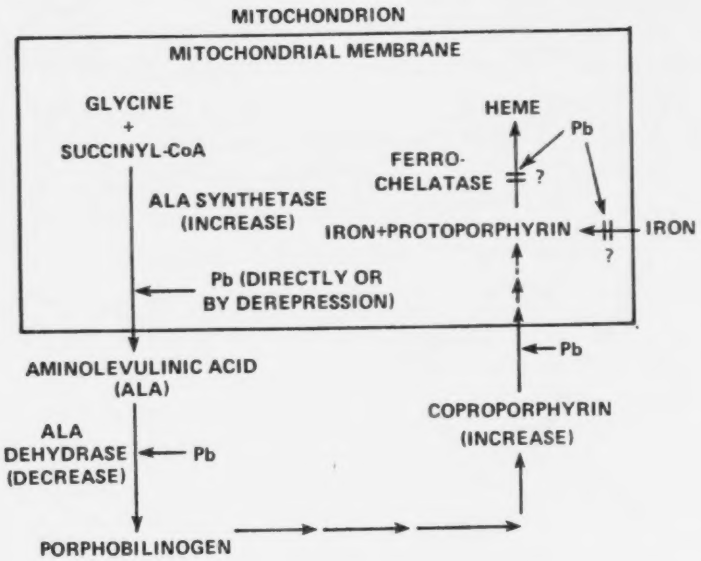

Figure 1-20. Effects of lead (Pb) on heme biosynthesis.

levels appears to be much less than the effect of ALA-D activity inhibition. ALA-D activity is significantly depressed at 40 μg/dl blood lead, the point at which ALA-S activity only begins to be affected.

Erythrocyte ALA-D activity is very sensitive to inhibition by lead. This inhibition is reversed by reactivation of the sulfhydryl group with agents such as dithiothreitol, zinc, or zinc and glutathione. Zinc levels that achieve reactivation, however, are well above physiological levels. Although zinc appears to offset the inhibitory effects of lead observed in animal studies and in human erythrocytes in vitro, lead workers exposed to both zinc and lead do not show significant changes in the relationship of ALA-D activity to blood lead when compared with workers exposed just to lead. Nor does the range of physiological zinc levels in nonexposed subjects affect ALA-D activity. In contrast, zinc deficiency in animals significantly inhibits ALA-D activity, with concomitant accumulation of ALA in urine. Because zinc deficiency has also been demonstrated to increase lead absorption, the possibility exists for the following dual effects of such deficiency on ALA-D activity: (1) a direct effect on activity due to reduced zinc availability; and (2) increased lead absorption leading to further inhibition of activity.

Erythrocyte ALA-D activity appears to be inhibited at virtually all blood lead levels measured so far, and any threshold for this effect in either adults or children remains to be determined. A further measure of this enzyme's sensitivity to lead is a report that rat bone marrow suspensions show inhibition of ALA-D activity by lead at a level of 0.1 μg/g suspension. Inhibition of ALA-D activity in erythrocytes apparently reflects a similar effect in other tissues. Hepatic ALA-D activity in lead workers was inversely correlated with erythrocyte activity as well as blood lead levels. Of significance are experimental animal data showing that (1) brain ALA-D activity is inhibited with lead exposure, and (2) this inhibition appears to occur to a greater extent in developing animals than in adults, presumably reflecting greater retention of lead in developing animals. In the avian brain, cerebellar ALA-D activity is affected to a greater extent than that of the cerebrum and, relative to lead concentration, shows inhibition approaching that occurring in erythrocytes.

Inhibition of ALA-D activity by lead is reflected by elevated levels of its substrate, ALA, in blood, urine, and soft tissues. Urinary ALA is employed extensively as an indicator of excessive lead exposure in lead workers. The diagnostic value of this measurement in pediatric screening, however, is limited when only spot urine collection is done; more satisfactory data are obtainable with 24-hr collections. Numerous independent studies document a direct correlation between blood lead and the logarithm of urinary ALA in human adults and children; the blood lead threshold for increases in urinary ALA is commonly accepted as 40 μg/dl. However, several studies of lead workers indicate that the correlation between urinary ALA and blood lead continues below this value; one study found that the slope of the dose-effect curve in lead workers depends on the level of exposure.

The health significance of lead-inhibited ALA-D activity and accumulation of ALA at lower lead exposure levels is controversial. The "reserve capacity" of ALA-D activity is such that only the level of inhibition associated with marked accumulation of the enzyme's substrate, ALA, in accessible indicator media may be significant. However, it is not possible to quantify at lower levels of lead exposure the relationship of urinary ALA to target tissue levels nor to relate the potential neurotoxicity of ALA at any accumulation level to levels in indicator media. Thus, the blood lead threshold for neurotoxicity of ALA may be different from that associated with increased urinary excretion of ALA.

Accumulation of protoporphyrin in erythrocytes of lead-intoxicated individuals has been recognized since the 1930s, but it has only recently been possible to quantitatively assess the nature of this effect via development of sensitive, specific microanalysis methods. Accumulation of protoporphyrin IX in erythrocytes results from impaired placement of iron (II) in the porphyrin moiety in heme formation, an intramitochondrial process mediated by ferrochelatase. In lead exposure, the porphyrin acquires a zinc ion in lieu of native iron, thus forming zinc protoporphyrin (ZPP), which is tightly bound in available heme pockets for the life of the erythrocytes. This tight sequestration contrasts with the relatively mobile nonmetal, or free, erythrocyte protoporphyrin (FEP) accumulated in the congenital disorder erythropoietic protoporphyria.

Elevation of erythrocyte ZPP has been extensively documented as exponentially correlated with blood lead in children and adult lead workers and is presently considered one of the best indicators of undue lead exposure. Accumulation of ZPP only occurs in erythrocytes formed during lead's presence in erythroid tissue; this results in a lag of at least several weeks before its buildup can be measured. The level of ZPP accumulation in erythrocytes of newly employed lead workers continues to increase after blood lead has already reached a plateau. This influences the relative correlation of ZPP and blood lead in workers with short exposure histories. Also, the ZPP level in blood declines much more slowly than blood lead, even after removal from exposure or after a drop in blood lead. Hence, ZPP level appears to be a more reliable indicator of continuing intoxication from lead resorbed from bone.

The threshold for detection of lead-induced ZPP accumulation is affected by the relative spread of blood lead and corresponding ZPP values measured. In young children (<4 yr old), the ZPP elevation associated with iron-deficiency anemia must also be considered. In adults, numerous studies indicate that the blood lead threshold for ZPP elevation is about 25-30 µg/dl. In children 10-15 years old, the threshold is about 16 µg/dl; for this age group, iron deficiency is not a factor. In one study, children over 4 years old showed the same threshold, 15.5 µg/dl, as a second group under 4 years old, indicating that iron deficiency was not a factor in the study. At 25 µg/dl blood lead, 50 percent of the children had significantly elevated FEP levels (2 standard deviations above the reference mean FEP).

At blood lead levels below 30-40 µg/dl, any assessment of the EP-blood lead relationship is strongly influenced by the relative analytical proficiency of measurements of both blood lead and EP. The types of statistical analyses used are also important. In a recent detailed statistical study involving 2004 children, 1852 of whom had blood lead values below 30 µg/dl, segmental line and probit analysis techniques were employed to assess the dose-effect threshold and dose-response relationship. An average blood lead threshold for the effect using both statistical techniques was 16.5 µg/dl for the full group and for those subjects with blood lead below 30 μg/dl; the effect of iron deficiency was tested for and removed. Of particular interest was the finding that blood lead values of 28.6 and 35.7 μg/dl corresponded to EP elevations of more than 1 or 2 standard deviations, respectively, above the reference mean in 50 percent of the children. Hence, fully half of the children had significant elevations of EP at blood lead levels around 30 μg/dl, which was the previously accepted cut-off value (now 25 μg/dl) for undue lead exposure specified by the Centers for Disease Control. From various reports, children and adult females appear to be more sensitive to lead's effects on EP accumulation at any given blood lead level; children are somewhat more sensitive than adult females.

Lead's effects on heme formation are not restricted to the erythropoietic system. Recent studies show that the reduction of serum 1,25-dihydroxyvitamin D seen with even low-level lead exposure is apparently the result of lead-induced inhibition of the activity of renal 1-hydroxylase, a cytochrome P-450-mediated enzyme. Reduction in activity of the hepatic enzyme tryptophan pyrrolase and concomitant increases in plasma tryptophan as well as brain tryptophan, serotonin, and hydroxyindoleacetic acid have been shown to be associated with lead-induced reduction of the hepatic heme pool. The heme-containing protein cytochrome P-450 (an integral part of the hepatic mixed-function oxygenase system) is affected in humans and animals by lead exposure, especially acute intoxication. Reduced P-450 content correlates with impaired activity of detoxifying enzyme systems such as aniline hydroxylase and aminopyrine demethylase. It is also responsible for reduced 6β-hydroxylation of cortisol in children having moderate lead exposure.

Studies of organotypic chick and mouse dorsal root ganglion in culture show that the nervous system has heme biosynthetic capability and that not only is such capability reduced in the presence of lead, but production of porphyrinic material is increased. In the neonatal rat, chronic lead exposure resulting in moderately elevated blood lead is associated with retarded increases in the hemoprotein cytochrome C and with disturbed electron transport in the developing cerebral cortex. These data parallel effects of lead on ALA-D activity and ALA accumulation in neural tissue. When both of these effects are viewed in the toxicokinetic context of increased retention of lead in both developing animals and children, there is an obvious and serious potential for impaired heme-based metabolic function in the nervous system of lead-exposed children.

As can be concluded from the above discussion, the health significance of ZPP accumulation rests with the fact that it is evidence of impaired heme and hemoprotein formation in many tissues that arises from entry of lead into mitochondria. Such evidence for reduced heme synthesis is consistent with a great deal of data documenting lead-associated effects on mitochondria. The relative value of the lead-ZPP relationship in erythropoietic tissue as an index of this effect in other tissues hinges on the relative sensitivity of the erythropoietic system compared with other organ systems. One study of rats exposed over their lifetime to low levels of lead demonstrated that protoporphyrin accumulation in renal tissue was already significant at levels of lead exposure which produced little change in erythrocyte porphyrin levels.

Other steps in the heme biosynthesis pathway are also known to be affected by lead, although these have not been as well studied on a biochemical or molecular level. Coproporphyrin levels are increased in urine, reflecting active lead intoxication. Lead also affects the activity of the enzyme uroporphyrinogen-I-synthetase in experimental animal systems, resulting in an accumulation of its substrate, porphobilinogen. The erythrocyte enzyme has been reported to be much more sensitive to lead than the hepatic species, presumably accounting for much of the accumulated substrate. Unlike the case with experimental animals, lead-exposed humans show no rise in urinary porphobilinogen, which is a differentiating characteristic of lead intoxication versus the hepatic porphyrias. Ferrochelatase is an intramitochondrial enzyme, and impairment of its activity either directly by lead or via impairment of iron transport to the enzyme is evidence of the presence of lead in mitochondria.

Anemia is a manifestation of chronic lead intoxication and is characterized as mildly hypochromic and usually normocytic. It is associated with reticulocytosis, owing to shortened cell survival, and the variable presence of basophilic stippling. Its occurrence is due to both decreased production and increased rate of destruction of erythrocytes. In young children (<4 yr old), iron deficiency anemia is exacerbated by lead uptake, and vice versa. Hemoglobin production is negatively correlated with blood lead in young children, in whom iron deficiency may be a confounding factor, as well as in lead workers. In one study, blood lead values that were usually below 80 μg/dl were inversely correlated with hemoglobin content. In these subjects no iron deficiency was found. The blood lead threshold for reduced hemoglobin content is about 50 μg/dl in adults and somewhat lower (~40 μg/dl) in children.

The mechanism of lead-associated anemia appears to be a combination of reduced hemoglobin production and shortened erythrocyte survival due to direct cell injury. Lead's effects on hemoglobin production involve disturbances of both heme and globin biosynthesis. The hemolytic component to lead-induced anemia appears to be caused by increased cell fragility and increased osmotic resistance. In one study using rats, the hemolysis associated with vitamin E deficiency, via reduced cell deformability, was exacerbated by lead exposure. The molecular basis for increased cell destruction rests with inhibition of (Na^+, K^+)-ATPase and pyrimidine-5'-nucleotidase. Inhibition of the former enzyme leads to cell "shrinkage" and inhibition of the latter results in impaired pyrimidine nucleotide phosphorolysis and disturbance of the activity of the purine nucleotides necessary for cellular energetics.

In lead intoxication, the presence of both basophilic stippling and anemia with a hemolytic component is due to inhibition by lead of the activity of pyrimidine-5'-nucleotidase (Py-5-N), an enzyme that mediates the dephosphorylation of pyrimidine nucleotides in the maturing erythrocyte. Inhibition of this enzyme by lead has been documented in lead workers, lead-exposed children, and experimental animal models. In one study of lead-exposed children, there was a negative correlation between blood lead and enzyme activity, with no clear response threshold. A related report noted that, in addition, there was a positive correlation between cytidine phosphate and blood lead and an inverse correlation between pyrimidine nucleotide and enzyme activity.

The metabolic significance of Py-5-N inhibition and cell nucleotide accumulation is that they affect erythrocyte stability and survival as well as potentially affect mRNA and protein synthesis related to globin chain synthesis. Based on one study of children, the threshold for the inhibition of Py-5-N activity appears to be about 10 μg/dl blood lead. Lead's inhibition of Py-5-N activity and a threshold for such inhibition are not by themselves the issue. Rather, the issue is the relationship of such inhibition to a significant level of impaired pyrimidine nucleotide metabolism and the consequences for erythrocyte stability and function. The relationship of Py-5-N activity inhibition by lead to accumulation of its pyrimidine nucleotide substrate is analogous to lead's inhibition of ALA-D activity and accumulation of ALA.

Tetraethyl lead and tetramethyl lead, components of leaded gasoline, undergo transformation in vivo to neurotoxic trialkyl metabolites as well as further conversion to inorganic lead. Hence, one might anticipate that exposure to such agents may result in effects commonly associated with inorganic lead, particularly in terms of heme synthesis and erythropoiesis. Various surveys and case reports show that the habit of sniffing leaded gasoline is associated with chronic lead intoxication in children from socially deprived backgrounds in rural or remote areas. Notable in these subjects is evidence of impaired heme biosynthesis, as indexed by significantly reduced ALA-D activity. In several case reports of frank lead toxicity from habitual leaded gasoline sniffing, effects such as basophilic stippling in erythrocytes and significantly reduced hemoglobin have also been noted.

The role of lead-associated disturbances of heme biosynthesis as a possible factor in neurological effects of lead is of considerable interest due to: (1) similarities between classical signs of lead neurotoxicity and several neurological components of the congenital disorder acute intermittent porphyria; and (2) some of the unusual aspects of lead neurotoxicity. There are three possible points of connection between lead's effects on heme biosynthesis and the nervous system. Associated with both lead neurotoxicity and acute intermittent porphyria is the common feature of excessive systemic accumulation and excretion of

ALA. In addition, lead neurotoxicity reflects, to some degree, impaired synthesis of heme and hemoproteins involved in crucial cellular functions; such an effect on heme is now known to be relevant within neural tissue as well as in non-neural tissue.

Available information indicates that ALA levels are elevated in the brains of lead-exposed animals and arise through *in situ* inhibition of brain ALA-D activity or through transport of ALA to the brain after formation in other tissues. ALA is known to traverse the blood-brain barrier. Hence, ALA is accessible to, or formed within, the brain during lead exposure and may express its neurotoxic potential.

Based on various *in vitro* and *in vivo* neurochemical studies of lead neurotoxicity, it appears that ALA can inhibit release of the neurotransmitter gamma-aminobutyric acid (GABA) from presynaptic receptors at which ALA appears to be very potent even at low levels. In an *in vitro* study, ALA acted as an agonist at levels as low as 1.0 μM ALA. This *in vitro* observation supports results of a study using lead-exposed rats in which there was inhibition of both resting and K^+-stimulated release of preloaded ^{3}H-GABA from nerve terminals. The observation that *in vivo* effects of lead on neurotransmitter function cannot be duplicated with *in vitro* preparations containing added lead is further evidence of an effect of some agent (other than lead) that acts directly on this function. Human data on lead-induced associations between disturbed heme synthesis and neurotoxicity, while limited, also suggest that ALA may function as a neurotoxicant.

A number of studies strongly suggest that lead-impaired heme production itself may be a factor in the lead's neurotoxicity. In porphyric rats, lead inhibits tryptophan pyrrolase activity owing to reductions in the hepatic heme pool, thereby leading to elevated levels of tryptophan and serotonin in the brain. Such elevations are known to induce many of the neurotoxic effects also seen with lead exposure. Of great interest is the fact that heme infusion in these animals reduces brain levels of these substances and also restores enzyme activity and the hepatic heme pool. Another line of evidence for the heme-basis of lead neurotoxicity is that mouse dorsal root ganglion in culture manifests morphological evidence of neural injury with rather low lead exposure, but such changes are largely prevented with co-administration of heme. Finally, studies also show that heme-requiring cytochrome C production is impaired along with operation of the cytochrome C respiratory chain in the brain when neonatal rats are exposed to lead.

Awareness of the interactions of lead and the vitamin D-endocrine system has been growing. A recent study has found that children with blood lead levels of 33-120 μg/dl showed significant reductions in serum levels of the hormonal metabolite 1,25-dihydroxyvitamin D ($1,25\text{-}(OH)_2D$). This inverse dose-response relationship was found throughout the range of measured blood lead values (12-120 μg/dl), and appeared to be the result of lead's effect on the production of the vitamin D hormone. The 1,25-$(OH)_2D$ levels of children with blood lead levels of 33-55 μg/dl corresponded to the levels that have been observed in children with severe renal dysfunction. At higher blood lead levels (>62 μg/dl), the 1,25-$(OH)_2D$ values were similar to those that have been measured in children with various inborn metabolic disorders. Chelation therapy of the lead-poisoned children (blood lead levels >62 μg/dl) resulted in a return to normal 1,25-$(OH)_2D$ levels within a short period.

In addition to its well known actions on bone remodeling and intestinal absorption of minerals, the vitamin D hormone has several other physiological actions at the cellular level. These include cellular calcium homeostasis in virtually all mammalian cells and associated calcium-mediated processes that are essential for cellular integrity and function. In addition, the vitamin D hormone has newly recognized functions that involve cell differentiation and essential immunoregulatory capacity. It is reasonable to conclude, therefore, that impaired production of 1,25-$(OH)_2D$ can have profound and pervasive effects on tissues and cells of diverse type and function throughout the body.

1.12.4 Neurotoxic Effects of Lead

An assessment of the impact of lead on human and animal neurobehavioral function raises a number of issues. Among the key points addressed here are the following: (1) the internal exposure levels, as indexed by blood lead levels, at which various neurotoxic effects occur; (2) the persistence or reversibility of such effects; and (3) populations that appear to be most susceptible to neural damage. In addition, the question arises as to the utility of using animal studies to draw parallels to the human condition.

Internal Lead Levels at which Neurotoxic Effects Occur. Markedly elevated blood lead levels are associated with the most serious neurotoxic effects of lead exposure (including severe, irreversible brain damage as indexed by the occurrence of acute or chronic encephalopathic symptoms, or both) in both humans and animals. For most adult humans, such damage typically does not occur until blood lead levels exceed 120 μg/dl. Evidence does exist, however, for acute encephalopathy and death occurring in some human adults at blood lead levels as low as 100 μg/dl. In children, the effective blood lead level for producing encephalopathy or death is lower, starting at approximately 80-100 μg/dl. It should be emphasized that, once encephalopathy occurs, death is not an improbable outcome, regardless of the quality of medical treatment available at the time of acute crisis. In fact, certain diagnostic or treatment procedures themselves may exacerbate matters and push the outcome toward fatality if the nature and severity of the problem are not diagnosed or fully recognized. It is also crucial to note the rapidity with which acute encephalopathic symptoms can develop or death can occur in apparently asymptomatic individuals or in those apparently only mildly affected by elevated lead body burdens. Rapid deterioration often occurs, with convulsions or coma suddenly appearing with progression to death within 48 hours. This strongly suggests that even in apparently asymptomatic individuals, rather severe neural damage probably exists at high blood lead levels even though it is not yet overtly manifested in obvious encephalopathic symptoms. This conclusion is further supported by numerous studies showing that overtly lead-intoxicated children with high blood lead levels, but not observed to manifest acute encephalopathic symptoms, are permanently cognitively impaired, as are most children who survive acute episodes of frank lead encephalopathy.

Recent studies show that overt signs and symptoms of neurotoxicity (indicative of both CNS and peripheral nerve dysfunction) are detectable in some human adults at blood lead levels as low as 40-60 μg/dl, levels well below blood lead concentrations previously thought to be "safe" for adult lead exposures. In addition, certain electrophysiological studies of peripheral nerve function in lead workers indicate that slowing of nerve conduction velocities in some peripheral nerves are associated with blood lead levels as low as 30-50 μg/dl (with no clear threshold for the effect being evident). These results are indicative of neurological dysfunctions occurring at relatively low lead levels in non-overtly lead intoxicated adults.

Other evidence confirms that neural dysfunctions exist in apparently asymptomatic children at similar or even lower levels of blood lead. The body of studies on low- or moderate-level lead effects on neurobehavioral functions in non-overtly lead intoxicated children, as discussed in Chapter 12, presents an array of data pointing to that conclusion. At high exposure levels, several studies point toward average 5-point IQ decrements occurring in asymptomatic children at average blood levels of 50-70 μg/dl. Other evidence is indicative of average IQ decrements of about 4 points being associated with blood levels in a 30-50 μg/dl range. Below 30 μg/dl, the evidence for IQ decrements is quite mixed, with some studies showing no significant associations with lead once other confounding factors are controlled. Still, the 1-2 point differences in IQ generally seen with blood lead levels in the 15-30 μg/dl range are suggestive of lead effects that are often dwarfed by other socio-hereditary factors. Moreover, a highly significant linear relationship between IQ and blood lead over the range of 6 to 47 μg/dl found in low-SES Black children indicates that IQ effects may be detected without evident threshold even at these low levels, at least in this population of children. In addition, other behavioral (e.g., reaction time, psychomotor performance) and electrophysiological (altered EEG patterns, evoked potential measures, and peripheral nerve conduction velocities are consistent with a dose-response function relating neurotoxic effects to lead exposure levels as low as 15-30 μg/dl and possibly lower. Although the comparability of blood lead concentrations across species is uncertain (see discussion below), studies show neurobehavioral effects in rats and monkeys at maximal blood lead levels below 20 μg/dl; some studies demonstrate residual effects long after lead exposure has terminated and blood lead levels have returned to approximately normal levels.

Timing, type, and duration of exposure are important factors in both animal and human studies. It is often uncertain whether observed blood lead levels represent the levels that were responsible for observed behavioral deficits or electrophysiological changes. Monitoring of lead exposures in pediatric subjects in all cases has been highly intermittent or nonexistent during the period of life preceding neurobehavioral assessment. In most studies of children, only one or two blood lead values are provided per subject. Tooth lead may be an important cumulative exposure index, but its modest, highly variable correlation to blood lead, FEP, or external exposure levels makes findings from various studies difficult to compare quantitatively. The complexity of the many important covariates and their interaction with dependent variable measures of modest validity, e.g., IQ tests, may also account for many of the discrepancies among the different studies.

The Question of Irreversibility. Little research on humans is available on persistence of effects. Some work suggests that mild forms of peripheral neuropathy in lead workers may be reversible after termination of lead exposure, but little is known regarding the reversibility of lead effects on central nervous system function in humans. A two-year follow-up study of 28 children of battery factory workers found a continuing relationship between blood lead levels and altered slow wave voltage of cortical slow wave potentials indicative of persisting CNS effects of lead; a five-year follow-up of some of the same children revealed the presence of altered brain stem auditory evoked potentials. Current population studies, however, will have to be supplemented by longitudinal studies of the effects of lead on development in order to address the issue of the reversibility or persistence of the neurotoxic effects of lead in humans more satisfactorily. (See the Addendum to this document for a discussion of recent results from prospective studies linking perinatal lead exposure to postnatal mental development.)

Various animal studies provide evidence that alterations in neurobehavioral function may be long-lived, with such alterations being evident long after blood lead levels have returned to control levels. These persistent effects have been demonstrated in monkeys as well as rats under a variety of learning performance test paradigms. Such results are also consistent with morphological, electrophysiological, and biochemical studies on animals that suggest lasting changes in synaptogenesis, dendritic development, myelin and fiber tract formation, ionic mechanisms of neurotransmission, and energy metabolism.

Early Development and the Susceptibility to Neural Damage. On the question of early childhood vulnerability, the neurobehavioral data are consistent with morphological and biochemical studies of the susceptibility of the heme biosynthetic pathway to perturbation by lead. Various lines of evidence suggest that the order of susceptibility to lead's effects is as follows: (1) young > adults and (2) female > male. Animal studies also have pointed to the perinatal period of ontogeny as a particularly critical time for a variety of reasons: (1) it is a period of rapid development of the nervous system; (2) it is a period where good nutrition is particularly critical; and (3) it is a period where the caregiver environment is vital to normal development. However, the precise boundaries of a critical period are not yet clear and may vary depending on the species and function or endpoint that is being assessed. One analysis of lead-exposed children suggests that differing effects on cognitive performance may be a function of the different ages at which children are subjected to neurotoxic exposures. Nevertheless, there is general agreement that human infants and toddlers below the age of three years are at special risk because of in utero exposure (see Addendum), increased opportunity for exposure because of normal mouthing behavior, and increased rates of lead absorption due to various factors, e.g., nutritional deficiences.

Utility of Animal Studies in Drawing Parallels to the Human Condition. Animal models are used to shed light on questions where it is impractical or ethically unacceptable to use human subjects. This is particularly true in the case of exposure to environmental toxins such as lead. In the case of lead, it has been effective and convenient to expose developing animals via their mothers' milk or by gastric gavage, at least until weaning. In many studies, exposure was continued in the water or food for some time beyond weaning. This approach simulates at least two features commonly found in human exposure: oral intake and exposure during early development. The preweaning period in rats and mice is of particular relevance in terms of parallels with the first two years or so of human brain development.

Studies using rodents and monkeys have provide a variety of evidence of neurobehavioral alteration induced by lead exposure. In most cases these effects suggest impairment in "learning," i.e, the processes of appropriately modifying one's behavior in response to information from the environment. Such behavior involves the ability to receive, process, and remember information in various forms. Some studies indicate behavioral alterations of a more basic type, such as delayed development of certain reflexes. Other evidence suggests changes affecting rather complex behavior in the form of social interactions.

Most of the above effects are evident in rodents and monkeys with blood lead levels exceeding 30 μg/dl, but some effects on learning ability are apparent even at maximum blood lead exposure levels below 20 μg/dl. Can these results with animals be generalized to humans? Given differences between humans, rats, and monkeys in heme chemistry, metabolism, and other aspects of physiology and anatomy, it is difficult to state what constitutes an equivalent internal exposure level (much less an equivalent external exposure level). For example, is a blood lead level of 30 μg/dl in a suckling rat equivalent to 30 μg/dl in a three-year-old child? Until an answer is available for this question, i.e., until the function describing the relationship of exposure indices in different species is available, the utility of animal models for deriving dose-response functions relevant to humans will be limited.

Questions also exist regarding the comparability of neurobehavioral effects in animals with human behavior and cognitive function. One difficulty in comparing behavioral endpoints such as locomotor activity is the lack of a consistent operational definition. In addition to the lack of standardized methodologies, behavior is notoriously difficult to "equate" or compare meaningfully across species because behavioral analogies do not demonstrate behavioral homologies. Thus, it is improper to assume, without knowing more about the responsible underlying neurological structures and processes, that a rat's performance on an operant conditioning schedule or a monkey's performance on a stimulus discrimination task corresponds to a child's performance on a cognitive function test. Nevertheless, interesting parallels in hyper-reactivity and increased response variability do exist between different species, and deficits in performance on various tasks are indicative of altered CNS functions, which are likely to parallel some type of altered CNS function in humans as well.

In terms of morphological findings, there are reports of hippocampal lesions in both lead-exposed rats and humans that are consistent with a number of behavioral findings suggesting an impaired ability to respond appropriately to altered contingencies for rewards. That is, subjects tend to persist in certain patterns of behavior even when changed conditions make the behavior inappropriate. Other morphological findings in animals, such as demyelination and glial cell decline, are comparable to human neuropathologic observations mainly at relatively high exposure levels.

Another neurobehavioral endpoint of interest in comparing human and animal neurotoxicity of lead is electrophysiological function. Alterations of electroencephalographic patterns and cortical slow wave voltage have been reported for lead-exposed children, and various electrophysiological alterations both _in vivo_ (e.g., in rat visual evoked response) and _in vitro_ (e.g., in frog miniature endplate potentials) have also been noted in laboratory animals. At this time, however, these lines of work have not converged sufficiently to allow for strong conclusions regarding the electrophysiological aspects of lead neurotoxicity.

Biochemical approaches to the experimental study of lead's effects on the nervous system have generally been limited to laboratory animal subjects. Although their linkage to human neurobehavioral function is at this point somewhat speculative, such studies do provide insight to possible neurochemical intermediaries of lead neurotoxicity. No single neurotransmitter system has been shown to be particularly sensitive to the effects of lead exposure; lead-induced alterations have been demonstrated in various neurotransmitters, including dopamine, norepinephrine, serotonin, and γ-aminobutyric acid. In addition, lead has been shown to have subcellular effects in the central nervous system at the level of mitochondrial function and protein synthesis.

Given the above-noted difficulties in formulating a comparative basis for internal exposure levels among different species, the primary value of many animal studies, particularly *in vitro* studies, may be in the information they can provide on basic mechanisms involved in lead neurotoxicity. A number of *in vitro* studies show that significant, potentially deleterious effects on nervous system function occur at *in situ* lead concentrations of 5 μM and possibly lower, suggesting that no threshold may exist for certain neurochemical effects of lead on a subcellular or molecular level. The relationship between blood lead levels and lead concentrations at such extra- or intracellular sites of action, however, remains to be determined. Despite the problems in generalizing from animals to humans, both the animal and the human studies show great internal consistency in that they support a continuous dose-response functional relationship between lead and neurotoxic biochemical, morphological, electrophysiological, and behavioral effects.

1.12.5 Effects of Lead on the Kidney

It has been known for more than a century that kidney disease can result from lead poisoning. Identifying the contributing causes and mechanisms of lead-induced nephropathy has been difficult, however, in part because of the complexities of human exposure to lead and other nephrotoxic agents. Nevertheless, it is possible to estimate at least roughly the range of lead exposure associated with detectable renal dysfunction in both human adults and children. Numerous studies of occupationally-exposed workers have provided evidence for lead-induced chronic nephropathy being associated with blood lead levels ranging from 40 to more than 100 μg/dl, and some are suggestive of renal effects, possibly occurring even at levels as low as 30 μg/dl. In children, the relatively sparse evidence available points to the manifestation of nephropathy only at quite high blood lead levels (usually exceeding 100-120 μg/dl). The current lack of evidence for nephropathy at lower blood lead levels in children may simply reflect the greater clinical concern with neurotoxic effects of lead intoxication in children or, possibly, that much longer-term lead exposures are necessary to induce nephropathy. The persistence of lead-induced nephropathy in children also remains to be more fully investigated, although a few studies indicate that children diagnosed as being acutely lead poisoned experience lead nephropathy effects lasting throughout adulthood.

Parallel results from experimental animal studies reinforce the findings in humans and help illuminate the mechanisms underlying such effects. For example, a number of transient effects in human and animal renal function are consistent with experimental findings of reversible lesions such as nuclear inclusion bodies, cytomegaly, swollen mitochondria, and increased numbers of iron-containing lysosomes in proximal tubule cells. Irreversible lesions such as interstitial fibrosis are also well documented in both humans and animals following chronic exposure to high doses of lead. Functional renal changes observed in humans have also been confirmed in animal model systems with respect to increased excretion of amino acids and elevated serum urea nitrogen and uric acid concentrations. The inhibitory effects of lead exposure on renal blood flow and glomerular filtration rate are currently less clear in experimental model systems; further research is needed to clarify the effects of lead on these functional parameters in animals. Similarly, while lead-induced perturbation of the renin-angiotensin system has been demonstrated in experimental animal models, further research is needed to clarify the exact relationships among lead exposure (particularly chronic low-level exposure), alteration of the renin-angiotensin system, and hypertension in both humans and animals.

On the biochemical level, it appears that lead exposure produces changes at a number of sites. Inhibition of membrane marker enzymes, decreased mitochondrial respiratory function/cellular energy production, inhibition of renal heme biosynthesis, and altered nucleic acid synthesis are the most marked changes to have been reported. The extent to which these mitochondrial alterations occur is probably mediated in part by the intracellular bioavailability of lead, which is determined by its binding to high-affinity kidney cytosolic proteins and deposition within intranuclear inclusion bodies.

Among the questions remaining to be answered more definitively about the effects of lead on the kidneys is the lowest blood lead level at which renal effects occur. In this regard it should be noted that recent studies in humans have indicated that the EDTA lead-mobilization test is the most reliable technique for detecting persons at risk for chronic nephropathy; blood lead measurements are a less satisfactory indicator because they may not accurately reflect cumulative absorption some time after exposure to lead has terminated. Other questions include the following: Can a distinctive lead-induced renal lesion be identified either in functional or histologic terms? What biologic measurements are most reliable for the prediction of lead-induced nephropathy? What is the incidence of lead nephropathy in the general population as well as among specifically defined subgroups with varying exposure? What is the mechanism of lead-induced hypertension and renal injury? What are the contributions of environmental and genetic factors to the appearance of renal injury due to lead? Conversely, the most difficult question of all may well be to determine the contribution of low levels of lead exposure to possible exacerbation of renal disease of non-lead etiologies.

1.12.6 Effects of Lead on Reproduction and Development

The most clear-cut data described in this section on reproduction and development are derived from studies employing high lead doses in laboratory animals. There is still a need for more critical research to evaluate the possible subtle toxic effects of lead on the fetus, using biochemical, ultrastructural, or behavioral endpoints. An exhaustive evaluation of lead-associated changes in offspring should include consideration of possible effects due to paternal lead burden as well. Neonatal lead intake via consumption of milk from lead-exposed mothers may also be a factor at times. Moreover, it must be recognized that lead's effects on reproduction may be exacerbated by other environmental factors (e.g., dietary influences, maternal hyperthermia, hypoxia, and co-exposure to other toxins).

There are currently no reliable data pointing to adverse effects in human offspring following lead exposure of fathers *per se*. Early studies of pregnant women exposed to high levels of lead indicated toxic, but not teratogenic, effects on the conceptus. Unfortunately, the collective human data regarding lead's effects on reproduction or *in utero* development currently do not lend themselves to accurate estimation of exposure-effect or no-effect levels. This is particularly true regarding lead effects on reproductive performance in women, which have not been well documented at low exposure levels. Still, prudence would argue for avoidance of lead exposures resulting in blood lead levels exceeding 25-30 µg/dl in pregnant women or women of child-bearing age in general, given the equilibration between maternal and fetal blood lead concentrations that occurs and the growing evidence for deleterious effects in young children as blood lead levels approach or exceed 25-30 µg/dl. Industrial exposures of men to lead at levels resulting in blood lead values of 40-50 µg/dl also appear to result in altered testicular function.

The paucity of human exposure data forces an examination of the animal studies for indications of threshold levels for effects of lead on the conceptus. It must be noted that the animal data are almost entirely derived from rodents. Based on these rodent data, it seems likely that fetotoxic effects have occurred in animals at chronic exposures to 600-800 ppm inorganic lead in the diet. Subtle effects appear to have been observed at 5-10 ppm in the drinking water, while effects of inhaled lead have been seen at levels of 10 mg/m^3. With multiple exposure by gavage, the lowest observed effect level is 64 mg/kg per day, and for exposure via injection, acute doses of 10-16 mg/kg appear effective. Since humans are most likely to be exposed to lead in their diet, air, or water, the data from other routes of exposure are of less value in estimating harmful exposures. Indeed, it appears that teratogenic effects occur in experimental animals only when the maternal dose is given by injection.

Although human and animal responses may be dissimilar, the animal evidence does document a variety of effects of lead exposure on reproduction and development. Measured or apparent changes in production of or response to reproductive hormones, toxic effects on the gonads, and toxic or teratogenic effects on the conceptus have all been reported. The animal data also suggest subtle effects on such parameters as metabolism and cell structure that should be monitored in human populations. Well-designed prospective human epidemiological studies (beyond the few presently available) involving large numbers of subjects are still needed. Such data could clarify the relationship of exposure periods, exposure durations, and blood lead concentrations associated with significant effects and are needed for estimation of no-effect levels as well. (Recent studies, most of which are prospective epidemiological investigations, on the relationship between relatively low-level lead exposure and effects on fetal and child development, along with supporting experimental evidence on possible underlying mechanisms are reviewed in an Addendum to this document.)

1.12.7 Genotoxic and Carcinogenic Effects of Lead

It is hard to draw clear conclusions concerning what role lead may play in the induction of human neoplasia. Epidemiological studies of lead-exposed workers provide no definitive findings. However, statistically significant elevations in respiratory tract and digestive system cancer in workers exposed to lead and other agents warrant some concern. Since lead acetate can produce renal tumors in some experimental animals, it seems reasonable to conclude that at least this particular lead compound should be regarded as a carcinogen and prudent to treat it as if it were also a human carcinogen (as concluded by the International Agency for Research on Cancer). However, this statement is qualified by noting that lead has been observed to increase tumorigenesis rates in animals only at relatively high concentrations, and therefore it does not appear to be a potent carcinogen. *In vitro* studies further support the genotoxic and carcinogenic role of lead, but also indicate that lead is not potent in these systems either.

1.12.8 Effects of Lead on the Immune System

Lead renders animals more susceptible to endotoxins and infectious agents. Host susceptibility and the humoral immune system appear to be particularly sensitive. As postulated in recent studies, the macrophage may be the primary immune target cell of lead. Lead-induced immunosuppression occurs in experimental animals at low lead exposures that, although not inducing overt toxicity, may nevertheless be detrimental to health. Available data provide good evidence that lead affects immunity, but additional studies are necessary to elucidate the actual mechanisms by which lead exerts its immunosuppressive action. Knowledge of the effects of lead on the human immune system is lacking and must be ascertained in order to determine permissible levels for human exposure. However, in view of the fact that lead affects immunity in laboratory animals and is immunosuppressive at very low dosages, its potential for serious effects in humans should be carefully considered.

1.12.9 Effects of Lead on Other Organ Systems

The cardiovascular, hepatic, gastrointestinal, and endocrine systems generally show signs of dysfunction at relatively high lead exposure levels. Consequently, in most clinical and experimental studies, attention has been primarily focused on more sensitive and vulnerable target organs, such as the hematopoietic and nervous systems. However, some work does suggest that humans and animals show significant increases in blood pressure following chronic exposure to low levels of lead (see Addendum to this document for a detailed discussion of the relationship between blood lead and blood pressure and the possible biological mechanisms which may be responsible for this association). It should also be noted that overt gastrointestinal symptoms associated with lead intoxication have been observed to occur in lead workers at blood lead levels as low as 40-60 µg/dl. These findings suggest that effects on the gastrointestinal and cardiovascular systems may occur at relatively low exposure levels but remain to be more conclusively demonstrated by further scientific investigations. Current evidence indicates that various endocrine processes may be affected by lead at relatively high exposure levels. However, little information exists on endocrine effects at lower exposure levels, except for alterations in vitamin-D metabolism previously discussed earlier as secondary to heme synthesis effects and occurring at blood lead levels ranging below 30 µg/dl to as low as 12 µg/dl. (Evidence relating endocrine function to various recently reported lead-associated effects on human fetal and child development, including effects on growth and stature, is reviewed in the Addendum to this document.)

1.13 EVALUATION OF HUMAN HEALTH RISKS ASSOCIATED WITH EXPOSURE TO LEAD AND ITS COMPOUNDS

1.13.1 Introduction

This section attempts to integrate key information and conclusions discussed in preceding sections into a coherent framework by which interpretation and judgments can be made concerning the risk to human health posed by present levels of lead contamination in the United States. In discussion of the various health effects of lead, the main emphasis is on the identification of those effects most relevant to various segments of the general U.S. population and the placement of such effects in a dose-effect/dose-response framework. With regard to the latter, a crucial issue has to do with the relative response of various segments of the population in terms of observed effect levels as indexed by some exposure indicator. Furthermore, it is of interest to assess the extent to which available information supports the existence of a continuum of effects as one proceeds across the spectrum of exposure levels. Discussion of data on the relative number or percentage of members of specific population groups that can be expected to experience a particular effect at various lead exposure levels (i.e., "responders") is also important in order to permit delineation of dose-response curves for the relevant effects in different segments of the population. These matters are discussed in Sections 1.13.4 and 1.13.5.

Melding of information from the sections on lead exposure, metabolism, and biological effects permits the identification of population segments at special risk in terms of physiological and other host characteristics, as well as heightened vulnerability to a given effect; these risk groups are discussed in Section 1.13.6. With demographic identification of individuals at risk, one may then draw upon population data from other sources to obtain a numerical picture of the magnitude of population groups at potential risk. This is also discussed in Section 1.13.6.

1.13.2 Exposure Aspects: Levels of Lead in Various Media of Relevance to Human Exposure

Human populations in the United States are exposed to lead in air, food, water, and dust. In rural areas, Americans not occupationally exposed to lead are estimated to consume 40-60 μg lead/day. This level of exposure is referred to as the baseline exposure for the American population because it is unavoidable except by drastic change in lifestyle or by regulation of lead in foods or ambient air. There are several environmental circumstances that can increase human exposures above baseline levels. Most of these circumstances involve the accumulation of atmospheric dusts in the work and play environments. A few, such as pica and family home gardening, may involve consumption of lead in chips of interior or exterior house paint.

Ambient Air Lead Levels. Monitored ambient air lead concentration values in the United States are contained in two principal data bases: (1) EPA's National Air Sampling Network (NASN), recently renamed National Filter Analysis Network (NFAN); and (2) EPA's National Aerometric Data Bank, consisting of measurements by state and local agencies in conjunction with compliance monitoring for the current ambient air lead standard.

NASN data for 1982, the most current year in the annual surveys, indicate that most of the urban sites show reported annual averages below 0.7 μg Pb/m^3, while the majority of the non-urban locations have annual figures below 0.2 μg Pb/m^3. Over the interval 1976-1982, there has been a downward trend in these averages, mainly attributable to decreasing lead content of leaded gasoline and the increasing usage of lead-free gasoline. Furthermore, examination of quarterly averages over this interval shows a typical seasonal variation, characterized by maximum air lead values in summer and minimum values in winter.

With respect to the particle size distribution of ambient air lead, EPA studies using cascade impactors in six U.S. cities have indicated that 60-75 percent of such air lead was associated with sub-micron particles. This size distribution is significant in considering the distance particles may be transported and the deposition of particles in the pulmonary compartment of the respiratory tract. The relationship between airborne lead at the monitoring station and the lead inhaled by humans is complicated by such variables as vertical gradients, relative positions of the source, monitor, and the person, and the ratio of indoor to outdoor lead concentrations. Personal monitors would probably be the most effective means to obtain an accurate picture of the amount of lead inhaled during the normal activities of an individual, but the information gained would be insignificant, considering that inhaled lead is generally only a small fraction of the total lead exposure, compared to the lead in food, beverages, and dust. The critical question in regard to airborne lead is how much lead becomes entrained in dust. In this respect, the existing monitoring network may provide an adequate estimate of the air concentration from which the rate of deposition can be determined.

Levels of Lead In Dust. The lead content of dusts can figure prominently in the total lead exposure picture for young children. Lead in aerosol particles deposited on rigid surfaces in urban areas (such as sidewalks, porches, steps, parking lots, etc.) does not undergo dilution compared to lead transferred by deposition onto soils. Lead in dust can approach extremely high concentrations and can accumulate in the interiors of dwellings as well as in the outside surroundings, particularly in urban areas.

Measurements of soil lead to a depth of 5 cm in areas of the United States were shown in one study to range from 150 to 500 μg/g dry weight close to roadways (i.e., within 8 meters). By contrast, lead in dusts deposited on or near heavily traveled traffic arteries show levels in major U.S. cities ranging up to 8000 μg/g and higher. In residential areas, exterior dust lead levels are approximately 1000 μg/g or less if contaminated only by atmospheric lead. Levels of lead in house dust can be significantly elevated; a study of house dust samples in Boston and New York City revealed levels of 1000-2000 μg/g. Some soils adjacent to houses with exterior lead-based paints may have lead concentrations greater than 10,000 μg/g.

Forty-four percent of the baseline consumption of lead by children is estimated to result from consumption of 0.1 g of dust per day, as noted earlier in Table 1-7 (and in Table 1-14 on a body weight basis). Ninety percent of this dust lead is of atmospheric origin. Dust also accounts for more than 90 percent of the additive lead attributable to living in an urban environment or near a smelter (see earlier Table 1-8).

Levels of Lead in Food. The route by which adults and older children in the baseline population of the United States receive the largest proportion of lead intake is through foods, with reported estimates of the dietary lead intake for Americans ranging from 40 to 60 μg/day. The added exposure from living in an urban environment is about 28 μg/day for adults and 91 μg/day for children, all of which can be attributed to atmospheric lead.

TABLE 1-14. RELATIVE BASELINE HUMAN LEAD EXPOSURES EXPRESSED PER KILOGRAM BODY WEIGHT*

	Total lead consumed, μg/day	Total lead consumed per kg body wt, μg/kg·day	Atmospheric lead per kg body wt, μg/kg·day
Child (2-yr-old)			
Inhaled air	0.5	0.05	0.05
Food and beverages	25.1	2.5	1.0
Dust	21.0	2.1	1.9
Total	46.6	4.65	2.95
Adult female			
Inhaled air	1.0	0.02	0.02
Food and beverages	32.0	0.64	0.25
Dust	4.5	0.09	0.06
Total	37.5	0.75	0.33
Adult male			
Inhaled air	1.0	0.014	0.014
Food and beverages	45.2	0.65	0.28
Dust	4.5	0.064	0.04
Total	50.7	0.73	0.334

*Body weights: 2-year-old child = 10 kg; adult female = 50 kg; adult male = 70 kg.

Source: This report.

Atmospheric lead may be added to food crops in the field or pasture, during transportation to the market, during processing, and during kitchen preparation. Metallic lead, mainly solder, may be added during processing and packaging. Other sources of lead, as yet undetermined, increase the lead content of food between the field and dinner table. American children, adult females, and adult males consume 19, 25, and 36 μg Pb/day, respectively, in milk and nonbeverage foods. Of these amounts, 49 percent is of direct atmospheric origin, 31 percent is of metallic origin, and 11 percent is of undetermined origin.

Processing of foods, particularly canning, can significantly add to their background lead content, although it appears that the impact of this is being lessened with the trend away from use of lead-soldered cans. The canning process can increase lead levels 8-to 10-fold higher than for the corresponding uncanned food items. Home food preparation can also be a source of additional lead in cases where food preparation surfaces are exposed to moderate amounts of high-lead household dust.

Lead Levels in Drinking Water. Lead in drinking water may result from contamination of the water source or from the use of lead materials in the water distribution system. Lead entry into drinking water from the latter is increased in water supplies which are plumbosolvent, i.e., with a pH below 6.5. Exposure of individuals occurs through direct ingestion of the water or via food preparation in such water.

The interim EPA drinking water standard for lead is 0.05 μg/g (50 μg/l) and several extensive surveys indicate that few public water supplies exceed this standard. For example, a survey of interstate carrier water supplies conducted by EPA showed that only 0.3 percent exceeded the standard, whereas mean levels of approximately 4.0 μg/l have been reported in 1971 and 1980 (as discussed in Section 7.2.3.1.1).

The major source of lead contamination of drinking water is the distribution system itself, particularly in older urban areas. Highest levels are encountered in "first-draw" samples, i.e., water sitting in the piping system for an extended period of time. In a large community water supply survey of 969 systems carried out in 1969-1970, it was found that the prevalence of samples exceeding 0.05 μg/g was greater where water was plumbo-solvent.

Most drinking water, and the beverages produced from drinking water, contain 0.007-0.011 μg lead/g. The exceptions are canned juices and soda pop, which range from 0.018 to 0.040 μg/g. About 15 percent of the lead consumed in drinking water and beverages is of direct atmospheric origin; 60 percent comes from solder and other metals.

Lead in Other Media. Flaking lead paint as well as paint chips and weathered powdered paint in and around deteriorated housing stock in urban areas of the Northeast and Midwest has long been recognized as a major source of lead exposure for young children residing there, particularly for children with pica. Census data, for example, indicate that there are approximately 27 million residential units in the United States built before 1940, many of which still contain lead-based paint. Individuals who are cigarette smokers may inhale significant amounts of lead in tobacco smoke. One study has indicated that the smoking of 30 cigarettes daily results in lead intake equivalent to that of inhaling lead in ambient air at a level of 1.0 μg/m^3.

Cumulative Human Lead Intake From Various Sources. Table 1-7 earlier illustrated the baseline of human lead exposures in the United States as described in detail in Chapter 7. These data show that atmospheric lead accounts for at least 40 percent of the baseline adult consumption and 60 percent of the daily consumption by a 2-yr-old child. These percentages are conservative estimates because a part of the lead of undetermined origin may originate from atmospheric lead not yet accounted for.

From Table 1-14, it can be seen that young children have a dietary lead intake rate that is fivefold greater than for adults, on a body weight basis. To these observations must be added that absorption rates for lead are higher in children than in adults by at least threefold. Overall, then, the rate of lead entry into the bloodstream of children, on a body weight basis, is estimated to be twice that of adults from the respiratory tract and six to nine times greater from the GI tract. Since children consume more dust than adults, the atmospheric fraction of the baseline exposure is sixfold higher for children than for adults, on a body weight basis. These differences generally tend to place young children at greater risk, in terms of relative amounts of atmospheric lead absorbed per kg body weight, than adults under any given lead exposure situation.

1.13.3 Lead Metabolism: Key Issues for Human Health Risk Evaluation

From the detailed discussion of those various quantifiable characteristics of lead toxicokinetics in humans and animals presented in Chapter 10, several clear issues emerge as being important for full evaluation of the human health risk posed by lead:

(1) Differences in systemic or internal lead exposure of groups within the general population in terms of such factors as age/development and nutritional status; and

(2) The relationship of indices of internal lead exposures to both environmental levels of lead and tissue levels/effects.

Item 1 provides the basis for identifying segments within human populations at increased risk in terms of exposure criteria, and is used along with additional information on relative sensitivity to lead health effects for identification of at-risk populations. Item 2 deals with the adequacy of current means of assessing internal lead exposure in terms of providing adequate margins of protection from lead exposures producing health effects of concern.

Differential Internal Lead Exposure Within Population Groups. Compared to adults, young children take in more lead through the gastrointestinal and respiratory tracts on a unit body weight basis, absorb a greater fraction of this lead intake, and also retain a greater proportion of the absorbed amount. Unfortunately, such amplification of these basic toxicokinetic parameters in children versus adults also occurs at the time when: (1) humans are developmentally more vulnerable to the effects of toxicants such as lead in terms of metabolic activity; and (2) the interactive relationships of lead with such factors as nutritive elements are such as to induce a negative course toward further exposure risk.

Typical of physiological differences in children versus adults in terms of lead exposure implications is a more metabolically active skeletal system in children. Turnover rates of bone elements such as calcium and phosphorus are greater in children than in adults, with correspondingly greater mobility of bone-sequestered lead. This activity is a factor in the observation that the skeletal system of children is relatively less effective as a depository for lead than in adults.

Metabolic demand for nutrients, particularly calcium, iron, phosphorus, and the trace nutrients, is such that widespread deficiencies of these nutrients exist, particularly among poor children. The interactive relationships of these elements with lead are such that deficiency states enhance lead absorption and/or retention. In the case of lead-induced reductions in 1,25-dihydroxyvitamin D, furthermore, there may exist an increasingly adverse interactive cycle between lead effects on 1,25-dihydroxyvitamin D and associated increased absorption of lead.

Quite apart from the physiological differences which enhance internal lead exposure in children is the unique relationship of 2- to 3-year-olds to their exposure setting by way of normal mouthing behavior; the extreme manifestation of this behavior is called pica. This behavior occurs in the same age group which studies have consistently identified as having a peak in blood lead. A number of investigations have addressed the quantification of this particular route of lead exposure, and it is by now clear that such exposure will dominate other routes when the child's surroundings, e.g., dust and soil, are significantly contaminated by lead.

Information provided in Chapter 10 also makes it clear that lead traverses the human placental barrier, with lead uptake by the fetus occurring throughout gestation. Such uptake of lead poses a potential threat to the fetus via an impact on the embryological developement of the central nervous and other systems. Hence, the only logical means of protecting the fetus from lead exposure is exposure control during pregnancy.

Within the general population, then, young children and pregnant women qualify as well-defined high-risk groups for lead exposure. In addition, certain emerging information (noted in Section 13.5 and described in detail in the Addendum to this document) indicates that increases in blood pressure are associated with blood lead concentrations ranging from $\geq$30-40 µg/dl down to possibly as low as 7 µg/dl; this association appears to be particularly robust in white males, aged 40-59. Occupational exposure to lead, particularly among lead workers, logically defines these individuals as also being in a high-risk category; work-place contact is augmented by those same routes and levels of lead exposure affecting the rest of the adult population. From a biological point of view, lead workers do not differ from the general adult population with respect to the various toxicokinetic parameters and any differences in exposure control--occupational versus non-occupational populations--as they exist, are based on factors other than toxicokinetics.

Indices of Internal Lead Exposure and Their Relationship To External Lead Levels and Tissue Burdens/Effects. Several points are of importance to consider in this area of lead toxicokinetics: (1) the temporal characteristics of indices of lead exposure; (2) the relationship of the indicators to external lead levels; (3) the validity of indicators of exposure in reflecting target tissue burdens; (4) the interplay between these indicators and lead in body compartments; and (5) those various aspects of the issue with particular reference to children.

At this time, blood lead is widely held to be the most convenient, if imperfect, index of both lead exposure and relative risk for various adverse health effects. In terms of exposure, however, it is generally accepted that blood lead is a temporally variable measure which yields an index of relatively recent exposure because of the rather rapid clearance of absorbed lead from the blood. Such a measure, then, is of limited usefulness in cases where exposure is variable or intermittent over time, as is often the case with pediatric lead exposure. Mineralizing tissues (specifically, deciduous teeth), on the other hand, accumulate lead over time in proportion to the degree of lead exposure, and analysis of this material provides an assessment integrated over a greater time period.

These two methods of assessing internal lead exposure have obvious shortcomings. A blood lead value will say little about any excessive lead intake at early periods, even though such remote exposure may have resulted in significant injury. On the other hand, whole tooth or dentine analysis is retrospective in nature and can only be done after the particularly vulnerable age in children--under 4-5 years--has passed. Such a measure, then, provides little utility upon which to implement regulatory policy or clinical intervention.

It may be possible to resolve the dilemmas posed by these existing methods by in situ analysis of teeth and bone lead, such that the intrinsic advantage of mineral tissue as a cumulative index is combined with measurement which is temporally concordant with on-going exposure. Work in several laboratories offers promise for such in situ analysis (see Chapters 9 and 10).

A second issue concerning internal indices of exposure and environmental lead is the relationship of changes in lead content of some medium with changes in blood content. Much of Chapter 11 is given over to description of the mathematical relationships of blood lead with lead in some external medium--air, food, water, etc.--without consideration of the biological underpinnings for these relationships.

Over a relatively broad range of lead exposure through some medium, the relationship of lead in the external medium to blood lead is curvilinear, such that relative change in blood lead per unit change in medium level generally becomes increasingly less as exposure increases. This behavior may reflect changes in tissue lead kinetics, reduced lead absorption, or increased excretion. With respect to changes in body lead distribution, the relative amount of whole blood lead in plasma increases significantly with increasing whole blood lead content; i.e., the plasma erythrocyte ratio increases. Limited animal data would suggest that changes in absorption may be one factor in this phenomenon. In any event, modest changes in blood levels with exposure at the higher end of this range are in no way to be taken as reflecting concomitantly modest changes in body or tissue lead uptake. Evidence continues to accumulate which suggests that an indicator such as blood lead is an imperfect measure of tissue lead burdens and of changes in such tissue levels in relation to changes in external exposure (see Figure 1-21).

In Chapter 10, it is pointed out that blood lead is logarithmically related to chelatable lead (the latter being a more useful measure of the potentially toxic fraction of body lead), such that a unit change in blood lead is associated with an increasingly larger amount of chelatable lead. One consequence of this relationship is that moderately elevated blood lead values will tend to mask the "margin of safety" in terms of mobile body lead burdens. Such masking is apparent in several studies of children where chelatable lead levels in children showing moderate elevations in blood lead overlapped those obtained in subjects showing frank plumbism, i.e., overt lead intoxication. In a multi-institutional survey involving several hundred children, it was found that a significant percentage of children with moderately elevated blood lead values had chelatable lead burdens which qualified them for medical treatment.

Related to the above is the question of the source of chelatable lead. It is noted in Chapter 10 that some sizable fraction of chelatable lead is derived from bone; this compels reappraisal of the notion that bone is an "inert sink" for otherwise toxic body lead. The notion of bone lead as toxicologically inert never did accord with what was known from studies of bone physiology, i.e., that bone is a "living" organ. The thrust of recent studies of chelatable lead, as well as interrelationships of lead and bone metabolism, supports the view that bone lead is actually an insidious source of long-term systemic lead exposure rather than a protective mechanism which permits significant lead contact in industrialized populations.

The complex interrelationships of lead exposure, blood lead, and lead in body compartments is of particular interest in considering the disposition of lead in young children. Since children take in more lead on a weight basis, and absorb and retain more of this lead than the adult, one might expect either that tissue and blood levels would be significantly elevated or that the child's skeletal system would be more efficient in lead sequestration. Average blood lead levels in young children are generally either similar to adult males or somewhat higher than for adult females. Limited autopsy data, furthermore, indicate that soft tissue levels in children are not markedly different from adults, whereas the skeletal system

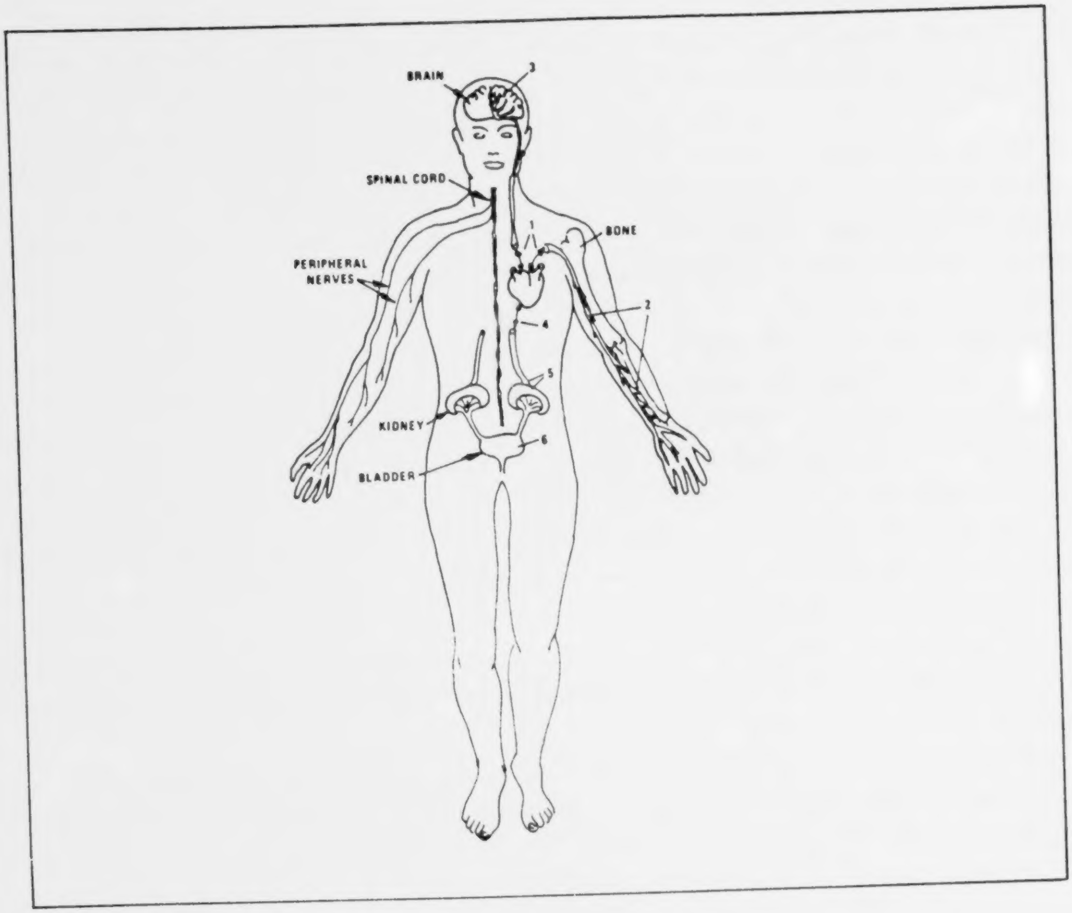

Figure 1-21. Illustration of main body compartments involved in partitioning, retention, and excretion of absorbed lead and selected target organs for lead toxicity. Inhaled and ingested lead circulates via blood (1) to mineralizing tissues such as teeth and bone (2), where long-term retention occurs reflective of cumulative past exposures. Concentrations of lead in blood circulating to "soft tissue" target organs such as brain (3), peripheral nerve, and kidney, reflect both recent external exposures and lead recirculated from internal reservoirs (e.g. bone). Blood lead levels used to index internal body lead burden tend to be in equilibrium with lead concentrations in soft tissues and, below 30 μg/dl, also generally appear to reflect accumulated lead stores. However, somewhat more elevated current blood lead levels may "mask" potentially more toxic elevations of retained lead due to relatively rapid declines in blood lead in response to decreased external exposure. Thus, provocative chelation of some children with blood leads of 30-40 μg/dl, for example, results in mobilization of lead from bone and other tissues into blood and movement of the lead (4) into kidney (5), where it is filtered into urine and excreted (6) at concentrations more typical of overtly lead-intoxicated children with higher blood lead concentrations.

shows an approximate twofold increase in lead concentration from infancy to adolescence. Neglected in this observation is the fact that the skeletal system in children grows at an exponential rate, so that skeletal mass increases 40-fold during the interval in childhood when bone lead levels increase twofold, resulting in an actual increase of approximately 80-fold in total skeletal lead. If the skeletal growth factor is taken into account, along with growth in soft tissue and the expansion of vascular fluid volumes, the question of lead disposition in children is better understood. Finally, limited animal data indicate that blood lead alterations with changes in lead exposure are poor indicators of such changes in target tissue. Specifically, it appears that abrupt reduction of lead exposure will be more rapidly reflected by decreases in blood lead than by decreased lead concentrations in such target tissues as the central nervous system, especially in the developing organism. This discordance may underlie the observation that severe lead neurotoxicity in children is associated with a rather broad range of blood lead values (see Section 12.4).

The above discussion of some of the problems with the use of blood lead in assessing target tissue burdens or the toxicologically active fraction of total body lead is really a summary of the inherent toxicokinetic problems with use of blood lead levels in defining margins of safety for avoiding internal exposure or undue risk of adverse effects. If, for example, blood lead levels of 30-50 μg/dl in "asymptomatic" children are associated with chelatable lead burdens which overlap those encountered in frank pediatric plumbism, as documented in several studies of lead-exposed children, then there is no margin of safety at these blood levels for severe effects which are not at all a matter of controversy. Were it both logistically feasible to do so on a large scale and were the use of chelants free of health risk to the subjects, serial provocative chelation testing would appear to be the better indicator of exposure and risk. Failing this, the only prudent alternative is the use of a large safety factor applied to blood lead which would translate to an "acceptable" chelatable burden. It is likely that this blood lead value would lie well below the currently accepted upper limit of 25 μg/dl, since the safety factor would have to be large enough to protect against frank plumbism as well as more subtle health effects seen with non-overt lead intoxication. This rationale from the standpoint of lead toxicokinetics is also in accord with the growing data base for dose-effect relationships of lead's effects on heme biosynthesis, erythropoiesis, and the nervous system in humans as detailed in Sections 12.3 and 12.4 (see also Section 1.13.4, below).

Further development and routine use of in situ mineral tissue testing at time points concordant with on-going exposure and the comparison of such results with simultaneous blood lead and chelatable lead measurement would be of significant value in further defining what level of blood lead is indeed an acceptable upper limit.

Proportional Contributions of Lead in Various Media to Blood Lead in Human Populations. The various mathematical descriptions of the relationship of blood lead to lead in individual media--air, food, water, dust, soil--are discussed in some detail in Chapter 11. Using values for lead intake/content of these media which appear to represent the current exposure picture for human populations in the United States, these relationships are further employed in this section to estimate proportional inputs to total blood lead levels in U.S. children. Such an exercise is of help in providing an overall perspective on which routes of exposure are of most significance in terms of contributions to blood lead levels, especially in urban children, which represent the population group in the United States at greatest risk for lead exposure and its toxic effects.

Table 1-15 tabulates the relative direct and indirect contributions of air lead to blood lead at different ambient air-lead levels for calculated typical background levels of lead from food, water, and dust for U.S. children. Calculations and assumptions used in deriving the estimates shown in Table 1-15 are summarized in footnotes to that table. The dietary contributions listed in the table, for example, are based on: (1) the estimated average background levels of lead (from non-air and air sources) in food ingested per day by U.S. children, as delineated in Table 7-19; and (2) the value of 0.16 µg/dl of blood lead increase per µg/day food lead intake found by Ryu et al. (1983) for infants. Similarly, values for other parameters used in Table 1-15 are obtained from work discussed in Chapters 7 and 11.

It is of interest to compare (1) estimated blood lead values predicted in Table 1-15 to occur at particular air lead concentrations with (2) actual blood lead levels observed for U.S. children living in areas with comparable ambient air concentrations. As an example, NHANES II survey results for children living in rural areas and urban areas of less than one million population or more than one million were presented in Table 11-5. For children (aged 0.5-5 yr) living in urban areas >1 million, the mean blood lead value was 16.8 µg/dl, a value representative of average blood lead levels nationwide for preschool children living in large urban areas during the NHANES survey period (1976 to February, 1980). Ambient air lead concentrations (quarterly averages) during the same time period (1976-1979) for a geographically diverse sample of large urban areas in the United States (population >1 million) are available from Table 7-2. The air lead levels during 1976-1979 averaged 1.08 µg/m^3 for all cities listed in Table 7-2 and 1.20 µg/m^3 for eight cities in the table that were included in the NHANES II study (i.e., Boston, New York, Philadelphia, Detroit, Chicago, Houston, Los Angeles, and Washington, DC). The Table 1-15 blood lead values of 12.6-14.6 µg/dl estimated for air lead levels of 1.0-1.25 µg/m^3 approximate the observed NHANES II average of 16.8 µg/dl for children in large urban areas with average air lead levels of 1.08-1.20 µg/m^3. The NHANES II blood lead values for preschool children would be expected to be somewhat higher than the estimates in Table 1-15 because the latter were derived from FDA data for 1981-1983, which

TABLE 1-15. CONTRIBUTIONS FROM VARIOUS MEDIA TO BLOOD LEAD LEVELS (μg/dl) OF U.S. CHILDREN (AGE = 2 YEARS): BACKGROUND LEVELS AND INCREMENTAL CONTRIBUTIONS FROM AIR

Source	Air lead, μg/m³						
	0	0.25	0.50	0.75	1.00	1.25	1.50
Background-non air							
Food, Water and Beverages[a]	2.37	2.37	2.37	2.37	2.37	2.37	2.37
Dust[b]	0.30	0.30	0.30	0.30	0.30	0.30	0.30
Subtotal	2.67	2.67	2.67	2.67	2.67	2.67	2.67
Background-air							
Food, Water and Beverages[c]	1.65	1.65	1.65	1.65	1.65	1.65	1.65
Ingested dust (with Pb deposited from air)[d]	0.00	1.57	3.09	4.70	6.27	7.84	9.40
Inhaled air[e]	0.00	0.50	1.00	1.50	2.00	2.50	3.00
Total	4.32	6.39	8.41	10.52	12.59	14.66	16.72

[a] From Table 7-19, (25.1 - 10.3) μg/day x (0.16 from Ryu et al., 1983) = 2.37 μg/dl.

[b] From Chapter 7, 1/10 dust not atmospheric. Using Angle et al. (1984) low area (Area S) for soil and house dust and their regression equation, we have: (1/10) x (97 μg/g x 0.00681 + 324 μg/g x 0.00718) = 0.30 μg/dl. Alternatively, the consumption from non air would be (1/10) x (97 μg/g soil dust + 324 μg/g house dust) x 0.05 grams ingested of each = 2.1 μg ingested. Using Ryu et al. (1983), 2.1 x 0.16 = 0.34 μg/dl added to blood.

[c] As in (a) above, but using 10.3 instead of (25.1 - 10.3) yields 1.67 μg/dl. Values are derived for component of background Pb in food from past deposition from air onto soil and into other media leading into human food chain (not expected to change much except over long-term).

[d] The regression equations of Angle et al. (1984) are used, as well as levels of soil dust and house dust in the low area (S) and high area (C) of that study. For example, the increase at 1.0 μg/m³ in air would result in increases in soil as follows:

$$\frac{1.00 - 0.29}{0.86 - 0.29} \times (519 - 97) = 526\ \mu g/g$$

Similarly the increase in house dust would be:

$$\frac{1.00 - 0.29}{0.86 - 0.29} \times (625 - 324) = 374\ \mu g/g$$

The effect on blood lead would be (526 x 0.00681) + (374 x 0.00718) = 6.27 μg/dl.

[e] Using the 2.0 slope from Angle et al. (1984), i.e., 1.93 rounded up.

were lower than the FDA values for the 1976-1980 NHANES II period (see Chapter 7). FDA data for food, water, and beverages for the 1976-1980 period are not in a form exactly comparable to the 1981-1983 data used in calculating background contributions in Table 1-15, but do suggest that lead levels in those media declined by about 20 percent from the 1976-1980 period to 1981-1983. If background contributions in Table 1-15 were corrected (i.e., increased by 20 percent) to be comparable to the 1976-1980 period, then the blood lead levels of children exposed to 1.25 µg/m^3 air lead would increase to 15.5 µg/dl, a value even closer to the mean of 16.8 µg/dl found for NHANES II children living in urban environments (>1 million) during 1976-1980.

1.13.4 Biological Effects of Lead Relevant to the General Human Population

It is clear from the wealth of available literature reviewed in Chapter 12 that there exists a continuum of biological effects associated with lead across a broad range of exposure. At rather low levels of lead exposure, biochemical changes, e.g., disruption of certain enzymatic activities involved in heme biosynthesis and erythropoietic pyrimidine metabolism, are detectable. Heme biosynthesis is a generalized process in mammalian species, including man, with importance for normal physiological functioning of virtually all organ systems. With increasing lead exposure, there are sequentially more intense effects on heme synthesis as well as a broadening of effects to additional biochemical and physiological mechanisms in various tissues. In addition to heme biosynthesis impairment at relatively low levels of lead exposure, disruption of normal functioning of the erythropoietic and nervous systems are among the earliest effects observed as a function of increasing lead exposure. With increasingly intense exposure, more severe disruption of the erythropoietic and nervous systems occur and additional organ systems are affected, resulting, for example, in manifestation of renal effects, disruption of reproductive functions, and impairment of immunological functions. At sufficiently high levels of exposure, the damage to the nervous system and other effects can be severe enough to result in death or, in some cases of non-fatal lead poisoning, long-lasting sequelae such as permanent mental retardation.

As discussed in Chapter 12 of this document, numerous new studies, reviews, and critiques concerning lead-related health effects have been published since the issuance of the earlier EPA Lead Criteria Document in 1977. Of particular importance for present criteria development purposes are those new findings, taken together with information available at the writing of the 1977 Criteria Document, which have bearing on the establishment of quantitative dose-effect or dose-response relationships for which can be potentially viewed as adverse health effects likely to occur among the general population at or near existing ambient air concentrations of lead in the United States. Key information regarding observed health effects and their implications are discussed below for adults and children.

For the latter group, children, emphasis is placed on the discussion of (1) heme biosynthesis effects, (2) certain other biochemical and hematological effects, and (3) the disruption of nervous system functions. All of these appear to be among those effects of most concern for potential occurrence in association with exposure to existing U.S. ambient air lead levels for the population group at greatest risk for lead-induced health effects (i.e., children ≤6 years old). Emphasis is also placed on the delineation of internal lead exposure levels, as defined mainly by blood lead (PbB) levels likely associated with the occurrence of such effects. Also discussed are characteristics of the subject effects that are of crucial importance with regard to the determination of which might reasonably be viewed as constituting "adverse health effects" in affected human populations.

Criteria for Defining Adverse Health Effects. Over the years, there have been superimposed on the continuum of lead-induced biological effects various judgments as to which specific effects observed in man constitute "adverse health effects". Such judgments not only involved medical consensus regarding the health significance of particular effects and their clinical management, but also incorporate societal value judgments. Such societal value judgments often vary depending upon the specific overall contexts to which they are applied, e.g., in judging permissible exposure levels for occupational versus general population exposures to lead. For some lead exposure effects, e.g., severe nervous system damage resulting in death or serious medical sequelae consequent to intense lead exposure, there exists little or no disagreement as to these being significant "adverse health effects." For many other effects detectable at sequentially lower levels of lead exposure, however, the demarcation lines as to which effects represent adverse health effects and the lead exposure levels at which they are accepted as occurring are neither sharp nor fixed, having changed markedly during the past several decades. That is, from an historical perspective, levels of lead exposure deemed to be acceptable for either occupationally-exposed persons or the general population have been steadily revised downward as more sophisticated biomedical techniques have revealed formerly unrecognized biological effects and concern has increased in regard to the medical and social significance of such effects.

It is difficult to provide a definitive statement of all criteria by which specific biological effects associated with any given agent can be judged to be "adverse health effects." Nevertheless, several criteria are currently well-accepted as helping to define which effects should be viewed as "adverse." These include the following: (1) impaired normal functioning of a specific tissue or organ system itself; (2) reduced reserve capacity of that tissue or organ system in dealing with stress due to other causative agents; (3) the reversibility/irreversibility of the particular effect(s); (4) the relative frequency of a given effect; (5) the presence of the effect in a vulnerable segment of the population; and (6) the cumulative or aggregate impact of various effects on individual organ systems on the overall functioning and well-being of the individual.

Examples of possible uses of such criteria in evaluating lead effects can be cited for illustrative purposes. For example, impairment of heme synthesis intensifies with increasing lead exposure until hemoprotein synthesis is inhibited in many organ systems, leading to reductions in such functions as oxygen transport, cellular energetics, neurotransmitter functions, detoxification of xenobiotic agents, and biosynthesis of important substances such as 1,25-dihydroxyvitamin D. In Figure 1-22, the far-ranging impact of lead on the body heme pool and associated disruption of many physiological processes is depicted, based on data discussed in Sections 12.2 and 12.3. Furthermore, inspection of Figure 1-22 reveals effects that can be viewed as intrinsically adverse, as well as those that reduce the body's ability to cope with other forms of toxic stress, e.g., reduced hepatic detoxification of many types of xenobiotics and, possibly, impairment of the immune system. The hepatic effect can also be cited as an example of reduced reserve capacity pertinent to consideration of the effects of lead, as the reduced capacity of the liver to detoxify certain drugs or other xenobiotic agents results from lead effects on hepatic detoxification enzyme systems.

In regard to the issue of reversibility/irreversibility of lead effects, there are really two dimensions to the issue that need to be considered, i.e.: (1) the biological reversibility or irreversibility characteristic of the particular effect in a given organism; and (2) the generally less-recognized concept of exposure reversibility or irreversibility. Severe central nervous system damage resulting from intense, high level lead exposure is generally accepted as an irreversible effect of lead exposure; however, the reversibility/irreversibility of certain more difficult-to-detect neurological effects occurring at lower lead exposure levels, remains a matter of some controversy. The concept of exposure reversibility/irreversibility can be illustrated by the case of urban children of low socioecomomic status showing disturbances in heme biosynthesis and erythropoiesis. Biologically, these various effects may be considered reversible; the extent to which actual reversibility occurs, however, is determined by the feasibility of removing these subjects from their particular lead exposure setting. If such removal from exposure is unlikely or does not occur, then such effects will logically persist and, de facto, constitute essentially irreversible effects.

The issues of frequency of effects and vulnerable segments of the population in whom these effects occur are intimately related. As discussed later in Section 1.13.6, young children--particularly inner city children--constitute a high risk group because they do show a high frequency of certain health effects as summarized below.

Dose-Effect Relationships for Human Adults. The lowest observed effect levels (in terms of blood lead concentrations) thus far credibly associated with particular health effects of concern for human adults in relation to specific organ systems or generalized physiological

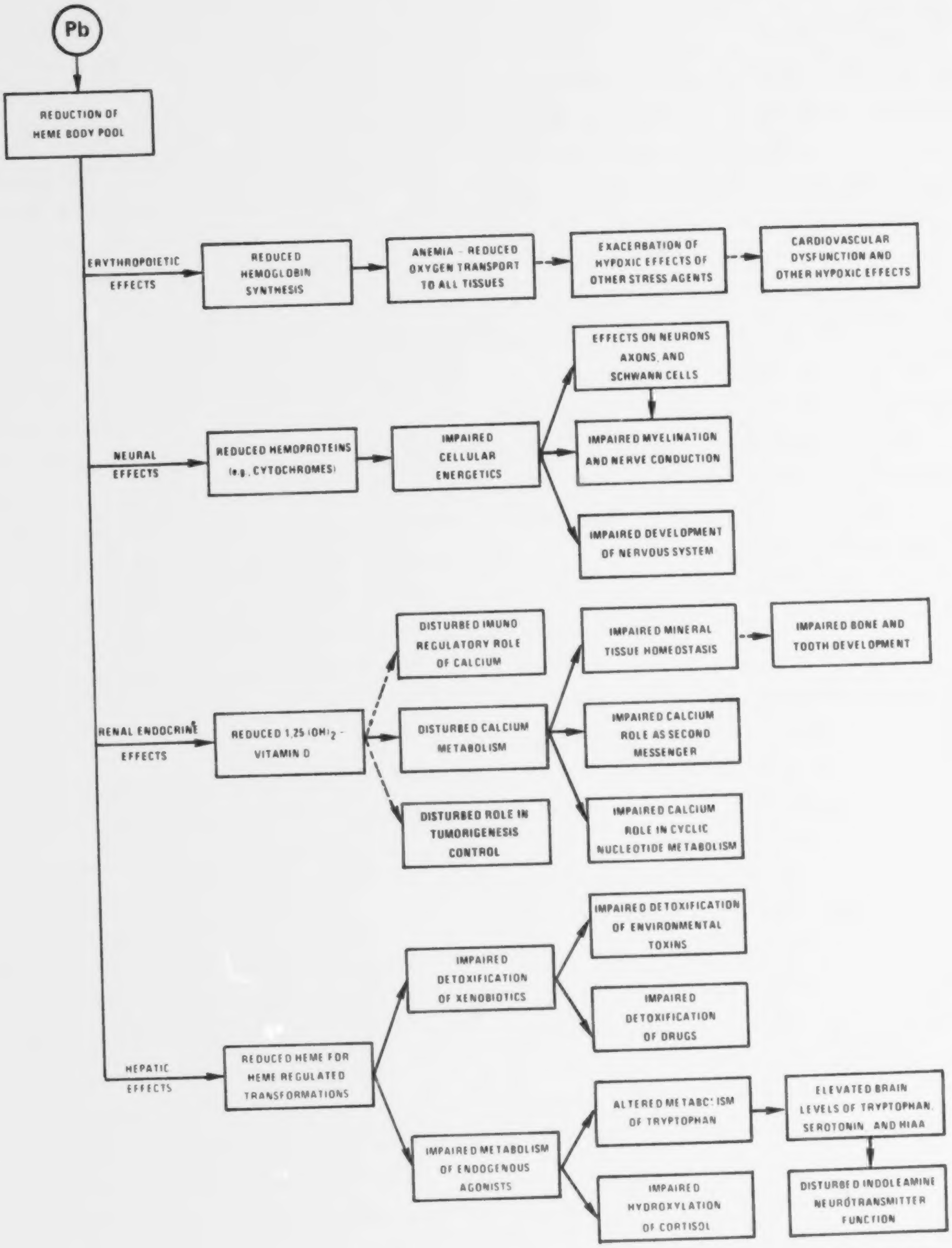
Pb
REDUCTION OF HEME BODY POOL
ERYTHROPOIETIC EFFECTS
REDUCED HEMOGLOBIN SYNTHESIS
ANEMIA - REDUCED OXYGEN TRANSPORT TO ALL TISSUES
EXACERBATION OF HYPOXIC EFFECTS OF OTHER STRESS AGENTS
CARDIOVASCULAR DYSFUNCTION AND OTHER HYPOXIC EFFECTS
NEURAL EFFECTS
REDUCED HEMOPROTEINS (e.g., CYTOCHROMES)
IMPAIRED CELLULAR ENERGETICS
EFFECTS ON NEURONS AXONS, AND SCHWANN CELLS
IMPAIRED MYELINATION AND NERVE CONDUCTION
IMPAIRED DEVELOPMENT OF NERVOUS SYSTEM
RENAL ENDOCRINE EFFECTS
REDUCED 1,25 (OH)2 - VITAMIN D
DISTURBED IMUNO REGULATORY ROLE OF CALCIUM
DISTURBED CALCIUM METABOLISM
DISTURBED ROLE IN TUMORIGENESIS CONTROL
IMPAIRED MINERAL TISSUE HOMEOSTASIS
IMPAIRED BONE AND TOOTH DEVELOPMENT
IMPAIRED CALCIUM ROLE AS SECOND MESSENGER
IMPAIRED CALCIUM ROLE IN CYCLIC NUCLEOTIDE METABOLISM
HEPATIC EFFECTS
REDUCED HEME FOR HEME REGULATED TRANSFORMATIONS
IMPAIRED DETOXIFICATION OF XENOBIOTICS
IMPAIRED DETOXIFICATION OF ENVIRONMENTAL TOXINS
IMPAIRED DETOXIFICATION OF DRUGS
IMPAIRED METABOLISM OF ENDOGENOUS AGONISTS
ALTERED METABOLISM OF TRYPTOPHAN
ELEVATED BRAIN LEVELS OF TRYPTOPHAN, SEROTONIN, AND HIAA
DISTURBED INDOLEAMINE NEUROTRANSMITTER FUNCTION
IMPAIRED HYDROXYLATION OF CORTISOL

Figure 1-22. Multi-organ impact of reductions of heme body pool by lead. Impairment of heme synthesis by lead (see Section 12.3) results in disruption of a wide variety of important physiological processes in many organs and tissues. Particularly well documented are erythropoietic, neural, renal-endocrine, and hepatic effects indicated above by solid arrows (——►). Plausible further consequences of heme synthesis interference by lead which remain to be more conclusively established are indicated by dashed arrows (---►).

processes, e.g., heme synthesis, are summarized in Table 1-16. That table should be viewed as representing lowest blood lead levels thus far credibly associated with unacceptable risk for a given effect occurring among at least some adults. As such, many other individuals may not experience the stated effect until distinctly higher blood lead levels are reached due to wide ranges of individual biological susceptibility, variations in nutritional status, and other factors.

The most serious effects associated with markedly elevated blood lead levels are severe neurotoxic effects that include irreversible brain damage, as indexed by the occurrence of acute or chronic encephalopathic symptoms observed in both humans and experimental animals. For most human adults, such damage typically does not occur until blood lead levels exceed 100-120 µg/dl. Often associated with encephalopathic symptoms at these or higher blood lead levels are severe gastrointestinal symptoms and objective signs of effects on several other organ systems. Precise threshold(s) for occurrence of overt neurological and gastrointestinal signs and symptoms of lead exposure in cases of subencephalopathic lead intoxication remain to be established, but such effects have been observed in adult lead workers at blood lead levels as low as 40-60 µg/dl, notably lower than levels earlier thought to be "safe" for adult lead exposure. Other types of health effects occur coincident with the above overt neurological and gastrointestinal symptoms indicative of marked lead intoxication. These range from frank peripheral neuropathies to chronic nephropathy and anemia.

Toward the lower range of blood lead levels associated with overt lead intoxication or somewhat below, less severe but important signs of impairment in normal physiological functioning in several organ systems are evident among apparently asymptomatic lead-exposed adults, including the following: (1) slowed nerve conduction velocities indicative of peripheral nerve dysfunction (at levels as low as 30-40 µg/dl); (2) altered testicular function (at 40-50 µg/dl); and (3) reduced hemoglobin production (at approximately 50 µg/dl) and other signs of impaired heme synthesis evident at still lower blood lead levels. All of these effects point toward a generalized impairment of normal physiological functioning across several different organ systems, which becomes abundantly evident as adult blood lead levels exceed 30-40 µg/dl. Evidence for impaired heme synthesis effects in blood cells exists at still lower blood lead levels in adults, as does evidence for elevated blood pressure in middle-aged white males (aged 40-59); the significance of this and evidence of impairment of other biochemical processes important in cellular energetics are discussed below in relation to children.

Dose-Effect Relationships for Children. Table 1-17 summarizes lowest observed effect levels for a variety of important health effects observed in children. Again, as for adults, it can be seen that lead impacts many different organ systems and biochemical/physiological

TABLE 1-16. SUMMARY OF LOWEST OBSERVED EFFECT LEVELS FOR KEY LEAD-INDUCED HEALTH EFFECTS IN ADULTS

Lowest observed effect level (PbB)*	Heme synthesis and hematological effects	Neurological effects	Effects on the kidney	Reproductive function effects	Cardiovascular effects
100-120 μg/dl		Encephalopathic signs and symptoms	Chronic nephropathy		
80 μg/dl	Frank anemia				
60 μg/dl				Female reproductive effects	
50 μg/dl	Reduced hemoglobin production	Overt subencephalopathic neurological symptoms		Altered testicular function	
40 μg/dl	Increased urinary ALA and elevated coproporphyrins	Peripheral nerve dysfunction (slowed nerve conduction)			
30 μg/dl					Elevated blood pressure (White males,) aged 40-59
25-30 μg/dl	Erythrocyte protoporphyrin (EP) elevation in males				
15-20 μg/dl	Erythrocyte protoporphyrin (EP) elevation in females				
<10 μg/dl	ALA-D inhibition				?

[*] PbB = blood lead concentrations.

Source: This report.

TABLE 1-17. SUMMARY OF LOWEST OBSERVED EFFECT LEVELS FOR KEY LEAD-INDUCED HEALTH EFFECTS IN CHILDREN

Lowest observed effect level (PbB)[a]	Heme synthesis and Hematological effects	Neurological effects	Renal system effects	Gastrointestinal effects
80-100 μg/dl		Encephalopathic signs and symptoms	Chronic nephropathy (aminoaciduria, etc.)	Colic, other overt gastrointestinal symptoms
70 μg/dl	Frank anemia			|
60 μg/dl		Peripheral neuropathies		↓ ?
50 μg/dl		| ↓ ?		
40 μg/dl	Reduced hemoglobin synthesis	Peripheral nerve dysfunction (slowed NCV's)		
	Elevated coproporphyrin	CNS cognitive effects (IQ deficits, etc.)		
	Increased urinary ALA	|		
30 μg/dl		? |	Vitamin D metabolism interference	
15 μg/dl	Erythrocyte protoporphyin elevation	Altered CNS electrophysiological responses	|	
10 μg/dl	ALA-D inhibition |	|	↓ ?	
	Py-5-N activity inhibition[b] ↓ ?	↓ ?		

[a] PbB = blood lead concentrations.
[b] Py-5-N = pyrimidine-5'-nucleotidase.

Source: This report.

processes across a wide range of exposure levels. Also, again, the most serious of these effects is the severe, irreversible central nervous system damage manifested in terms of encephalopathic signs and symptoms. In children, effective blood lead levels for producing encephalopathy or death are lower than for adults, starting at approximately 80-100 µg/dl. Permanent severe mental retardation and other marked neurological deficits are among lasting neurological sequelae typically seen in cases of non-fatal childhood lead encephalopathy. Other overt neurological signs and symptoms of subencephalopathic lead intoxication are evident in children at lower blood lead levels (e.g., peripheral neuropathies have been detected in some children at levels as low as 40-60 µg/dl). Chronic nephropathy, indexed by aminoaciduria, is most evident at high exposure levels producing blood lead levels over 100 µg/dl, but may also exist at lower levels (e.g., 70-80 µg/dl). In addition, colic and other overt gastrointestinal symptoms clearly occur at similar or still lower blood lead levels in children, at least down to 60 µg/dl. Frank anemia is also evident by 70 µg/dl, representing an extreme manifestation of reduced hemoglobin synthesis observed at blood lead levels as low as 40 µg/dl, along with other signs of marked heme synthesis inhibition at that exposure level. All of these effects are reflective of the widespread marked impact of lead on the normal physiological functioning of many different organ systems and some are evident in children at blood lead levels as low as 40 µg/dl. All of these effects are widely accepted as clearly adverse health effects.

Additional studies demonstrate evidence for further, important health effects occurring in non-overtly lead-intoxicated children at similar or lower blood lead levels than those indicated above for overt intoxication effects. Among the most important of the effects discussed in Chapter 12 are neuropsychological and electrophysiological effects evaluated as being associated with low-level lead exposures in non-overtly lead-intoxicated children. Indications of peripheral nerve dysfunction, indexed by slowed nerve conduction velocities (NCV), have been shown in children down to blood lead levels as low as 30 µg/dl. As for CNS effects, none of the available studies on the subject, individually, can be said to prove conclusively that significant cognitive (IQ) or behavioral effects occur in children at blood lead levels <30 µg/dl. However, the most recent neurobehavioral studies of CNS cognitive (IQ) effects collectively demonstrate associations between neuropsychologic deficits and low-level lead exposures in young children resulting in blood lead levels ranging to below 30 µg/dl. The magnitudes of average observed IQ deficits generally appear to be approximately 5 points at mean blood lead levels of 50-70 µg/dl, about 4 points at mean blood lead levels of 30-50 µg/dl, and 1-2 points at mean blood lead levels of 15-30 µg/dl. Somewhat larger decrements have been reported for the latter blood lead range among children of lower socioeconomic status families.

Additional recent studies have obtained results at blood lead values mainly in the 15-30 μg/dl range indicative of small, but not unimportant, effects of lead on the ability to focus attention, appropriate social behavior, and other types of behavioral performance. However, due to specific methodological problems with each of these various studies (as noted in Chapter 12), much caution is warranted that precludes conclusive acceptance of the observed effects being due to lead rather than other (at times uncontrolled for) potentially confounding variables. This caution is particularly warranted in view of other well-conducted studies that have appeared in the literature which did not find statistically significant associations between lead and similar effects at blood lead levels below 30 μg/dl. Still, because such latter studies even found some small effects remaining after correction for confounding factors, lead cannot be ruled out as an etiological factor contributing to the induction of such effects in the 15-30 μg/dl range, based on existing published studies.

Also of considerable importance are studies which provide evidence of changes in EEG brain wave patterns and CNS evoked potential responses in non-overtly lead intoxicated children. The work of Burchfiel et al. (1980) indicates significant associations between IQ decrements, EEG pattern changes, and lead exposures among children with average blood lead levels falling in the range of 30-50 μg/dl. Research results provided by Otto et al. (1981, 1982, 1983) also demonstrate clear, statistically significant associations between electrophysiological (SW voltage) changes and blood lead levels in the range of 30-55 μg/dl and analogous associations at blood lead levels below 30 μg/dl (with no evident threshold down to 15 μg/dl or somewhat lower). In this case, the presence of electrophysiological changes observed upon follow-up of some of the same children two years and five years later suggests persistence of such effects even in the face of later declines in blood lead levels and, therefore, possible long-term persistence of the observed electrophysiological CNS changes. However, the reported electrophysiological effects in this case were not found to be significantly associated with IQ decrements.

While the precise medical or health significance of the neuropsychological and electrophysiological effects found by the above studies to be associated with low-level lead exposures is difficult to fully define at this time, the IQ deficits and other behavioral changes likely impact the intellectual development, school performance, and social development of the affected children sufficiently so as to be regarded as adverse. This is especially true if such impaired intellectual development or school performance and disrupted social development are reflective of persisting, long-term effects of low-level lead exposure in early childhood. The issue of persistence of such lead effects still remains to be more clearly resolved, with some study results reviewed in Chapter 12 and mentioned above suggesting relatively short-lived or markedly decreasing lead effects on neuropsychological functions over a few years from early to later childhood and other studies suggesting that significant low-level lead-induced neurobehavioral and EEG effects may, in fact, persist into later childhood. Despite any remaining ambiguities of the above type, however, the medical community has highlighted (CDC, 1985) lead-induced neurobehavioral effects (e.g., IQ deficits and other neuropsychologic effects) as one basis for viewing pediatric blood lead levels below 25-30 µg/dl as being associated with unacceptable risk for lead-induced toxicity.

In regard to additional studies reviewed in Chapter 12 concerning the neurotoxicity of lead, certain evidence exists which suggests that neurotoxic effects may be associated with lead-induced alterations in heme synthesis, resulting in an accumulation of ALA in brain which affects CNS GABA synthesis, binding, and/or inactivation by neuronal reuptake after synaptic release. Also, available experimental data suggest that these effects may have functional significance in the terms of this constituting one mechanism by which lead may increase the sensitivity of rats to drug-induced seizures and, possibly, by which GABA-related behavioral or physiological control functions are disrupted. Unfortunately, the available research data do not allow credible direct estimates of blood lead levels at which such effects might occur in rats, other non-human mammalian species, or man. Inferentially, however, one can state that threshold levels for any marked lead-induced ALA impact on CNS GABA mechanisms are most probably at least as high as blood lead levels at which significant accumulations of ALA have been detected in erythrocytes or non-blood soft tissues (see below). Regardless of any dose-effect levels inferred, though, the functional and/or medical significance of lead-induced ALA effects on CNS mechanisms at low levels of lead exposure remains to be more fully determined and cannot, at this time, be unequivocably seen as an adverse health effect.

Research concerning lead-induced effects on heme synthesis also provides information of importance in evaluating what blood lead levels are associated with significant health effects in children. As discussed earlier, in Chapter 12 and Section 13.4, lead affects heme synthesis at several points in its metabolic pathway, with consequent impact on the normal functioning of many body tissues. The activity of the enzyme ALA-S, catalyzing the rate-limiting step of heme synthesis, does not appear to be significantly affected until blood lead levels reach or exceed approximately 40 µg/dl. The enzyme ALA-D, which catalizes the conversion of ALA to porphobilinogen as a further step in the heme biosynthetic pathway, appears to be affected at much lower blood lead levels as indexed directly by observations of ALA-D inhibition or indirectly in terms of consequent accumulations of ALA in blood and non-blood tissues. More specifically, inhibition of erythrocyte ALA-D activity has been observed in humans and other mammalian species at blood lead levels even below 10-15 µg/dl, with no clear threshold evident. Correlations between erythrocyte and hepatic ALA-D activity inhibition in lead workers at blood lead levels in the range of 12-56 µg/dl suggest that ALA-D activity in soft tissues (e.g., brain, liver, kidney, etc.) may be inhibited at similar blood lead levels at which erythrocyte ALA-D activity inhibition occurs, resulting in accumulations of ALA in both blood and soft tissues.

Some studies indicate that increases in both blood and urinary ALA occur below the current commonly-accepted blood lead level of 40 µg/dl. Such increases in blood and urinary ALA are detectable in humans at blood lead levels below 30 µg/dl, with no clear threshold evident down to 15-20 µg/dl, although other data exist which fail to show any relationship below 40 µg/dl blood lead. Other studies have demonstrated significant elevations in rat brain, spleen, and kidney ALA levels consequent to acute or chronic lead exposure, but no clear blood lead levels can yet be specified at which such non-blood tissue ALA increases occur in humans. It is reasonable to assume, however, that ALA increases in non-blood tissues likely begin to occur at roughly the same blood lead levels associated with increases in erythrocyte ALA levels.

Lead also affects heme synthesis beyond metabolic steps involving ALA, leading to the accumulation of porphyrin in erythrocytes as the result of impaired iron insertion into the porphyrin moiety to form heme. The porphyrin acquires a zinc ion in lieu of the native iron, and the resulting accumulation of blood zinc protoporphyrin (ZPP) tightly bound to erythrocytes for their entire life (120 days) represents a commonly employed index of lead exposure for medical screening purposes. The threshold for elevation of erythrocyte protoporphyrin (EP) levels is well-established as being 25-30 µg/dl in adults and approximately 15 µg/dl for young children, with significant EP elevations (>1-2 standard deviations above reference normal EP mean levels) occurring in 50 percent of all children studied as blood lead approaches or moderately exceeds 30 µg/dl.

Medically, small increases in EP levels were previously not viewed as being of great concern at initial detection levels around 15-20 µg/dl in children. However, EP increases become more worrisome when markedly greater, significant elevations occur as blood lead levels reach 20 to 30 µg/dl and additional signs of significantly deranged heme synthesis begin to appear, along with indications of functional disruption of various organ systems. Previously, such other signs of significant organ system functional disruptions had only been credibly detected at blood lead levels distinctly in excess of 30 µg/dl, e.g., inhibition of hemoglobin synthesis starting at 40 µg/dl and significant nervous system effects at 50-60 µg/dl. This served as a basis for CDC's 1978 statement establishing 30 µg/dl blood lead as a criteria level for undue lead exposure for young children. At the present time, however, the medical community (CDC, 1985) accepts EP elevations associated with PbB levels of 25 µg/dl or higher as being unacceptable in pediatric populations.

Recently, it has also been demonstrated in children that lead is negatively correlated with circulating levels of the vitamin D hormone, 1,25-dihydroxyvitamin D, with the negative association existing down to 12 μg/dl of blood lead. This effect of lead is of considerable significance on two counts: (1) altered levels of 1,25-$(OH)_2$-vitamin D not only impact calcium homeostasis (affecting mineral metabolism, calcium as a second messenger, and calcium as a mediator of cyclic nucleotide metabolism), but also likely impact its known role in immunoregulation and mediation of tumorigenesis; and (2) the effect of lead on 1,25-$(OH)_2$-vitamin D is a particularly robust one, with blood lead levels of 30-50 μg/dl resulting in decreases in the hormone that overlap comparable degrees of decrease seen in severe kidney injury or certain genetic diseases.

Erythrocyte Py-5-N activity in children has also been demonstrated to be negatively impacted by lead at exposures resulting in blood lead levels markedly below 30 μg/dl (i.e., to levels below 5 μg/dl with no evident threshold). Extensive reserve capacity exists for this blood enzyme, such that it is not markedly depleted until blood lead levels reach approximately 30-40 μg/dl, arguing for the Py-5-N effect in and of itself as perhaps not being particularly adverse until such blood lead levels are reached. However, the observation of Py-5-N inhibition is a better indicator of more widespread impacts on pyrimidine metabolism in general in additional organs and tissues besides blood, such that lead exposures lower than 30 μg/dl resulting in measurable Py-5-N inhibition in erythrocytes may be of greater medical concern when viewed from this broader perspective.

Also adding to the concern about relatively low lead exposure levels are the results of an expanding array of animal toxicology studies which demonstrate: (1) the persistence of lead-induced neurobehavioral alterations well into adulthood long after termination of perinatal lead exposure early in development of several mammalian species; (2) evidence for uptake and retention of lead in neural and non-neuronal elements of the CNS, including long-term persistence in brain tissues after termination of external lead exposure and blood lead levels return to "normal"; and (3) evidence from various in vivo and in vitro studies indicating that, at least on a subcellular-molecular level, no threshold may exist for certain neurochemical effects of lead.

Given the above new evidence that is now available, indicative of significant lead effects on nervous system functioning and other important physiological processes as blood lead levels increase above 15-20 μg/dl and reach 20 to 30 μg/dl, the rationale for considering 30 μg/dl as a "maximum safe" blood lead level (as was the case in setting the 1978 EPA lead NAAQS) was called into question and substantial impetus provided for revising the criteria level downward. At this time, it is difficult to identify specifically what blood lead criteria level would be appropriate in view of the existing medical information. Clearly, however, 30 μg/dl does not afford any margin of safety before blood lead levels are reached that are associated with unacceptable risk of notable adverse health effects occurring in some children. This is based on at least two grounds: (1) blood lead levels in the 30-40 μg/dl range are now known to "mask", for some children, markedly elevated chelatable body lead burdens that are comparable to lead burdens seen in other children displaying overt signs and symptoms of lead intoxication and (2) blood lead levels in the 30-40 μg/dl range are also associated with the onset of deleterious effects in several organ systems which are either individually or collectively seen as being adverse. These and other considerations have led the medical community (CDC, 1985) to define 25 μg/dl PbB as a level associated with unacceptable risk for pediatric lead toxicity.

At levels below 25-30 μg/dl, many of the different smaller effects reported as being associated with lead exposure might be argued as separately not being of clear medical significance, although each are indicative of interference by lead with normal physiological processes. On the other hand, the collective impact of all of the observed effects (representing potentially impaired functioning and depleted reserve capacities of many different tissues and organs) can, at some point distinctly below 25-30 μg/dl, be seen as representing an adverse pattern of effects worthy of avoidance with some added margin of safety. The onset of signs of detectable heme synthesis impairment in many different organ systems at blood lead levels starting around 10-15 μg/dl, along with indications of increasing degrees of pyrimidine metabolism interference and signs of altered nervous system activity, could be viewed as such a point. Or, alternatively, the collective impact of such effects might be argued as becoming sufficiently adverse to warrant avoidance (with a margin of safety) only when the various effects come to represent marked deviations from normal as blood lead levels exceed 20-25 μg/dl.

The frequency of occurrence of various effects among individual, affected children at various blood lead levels may have important bearing on the ultimate resolution of the above issue regarding the definition of blood lead levels associated with adverse health effects in pediatric populations. The porportion of children likely affected (i.e., "responders") in terms of experiencing particular types of effects at various lead levels is also an important consideration. Some information bearing on this latter point is discussed next.

1.13.5 Dose-Response Relationships for Lead Effects in Human Populations

Information summarized in the preceding section dealt with the various biological effects of lead germane to the general population and included comments about the various levels of blood lead observed to be associated with the measurable onset of these effects in various population groups.

As indicated above, inhibition of ALA-D activity by lead occurs at virtually all blood lead levels measured in subjects residing in industrialized countries. If any threshold for ALA-D inhibition exists, it lies somewhere below 10 μg Pb/dl in blood lead. Also, statistically significant reduction in hemoglobin production occurs at a lower blood lead level in children (40 μg/dl) than in adults (50 μg/dl).

Elevation in erythrocyte protoporphyrin for a given blood lead level is greater in children and women than in adult males, children being somewhat more sensitive than women. The current threshold for detectable EP elevation in terms of blood lead levels for children was estimated at approximately 16-17 μg/dl in the recent studies of Piomelli et al. (1982). In adult males, the corresponding blood lead value is 25-30 μg/dl.

Coproporphyrin elevation in urine first occurs at a blood lead level of 40 μg/dl and this threshold appears to apply for both children and adults. It also appears that urinary ALA shows a correlation with blood lead levels to below 40 μg/dl, but since there is no clear agreement as to the meaning of elevated ALA-U below 40 μg/dl, this value is taken as the threshold for pronounced excretion of ALA into urine. This value appears to apply to both children and adults. Whether this blood lead level represents a threshold for the potential neurotoxicity of circulating ALA cannot now be stated and requires further study.

A number of investigators have attempted to quantify more precisely dose-population response relationships for some of the above lead effects in human populations. That is, they have attempted to define the proportion of a population exhibiting a particular effect at a given blood lead level. To date, such efforts at defining dose-response relationships for lead effects have been mainly limited to the following effects of lead on heme biosynthesis: inhibition of ALA-D activity; elevation of EP; and urinary excretion of ALA.

Dose-population response relationships for EP in children have been analyzed in detail by Piomelli et al. (1982) and the corresponding plot at 2 levels of elevation (>1 S.D., >2 S.D.) is shown in Figure 1-23 using probit analysis. It can be seen that blood lead levels in half of the children showing EP elevations at >1 and 2 S.D.'s closely bracket the blood lead level taken as the high end of "normal" (i.e., 30 μg/dl). Dose-response curves for adult men and women as well as children prepared by Roels et al. (1976) are set forth in Figure 1-24. In Figure 1-24, it may be seen that the dose-response for children remains greater across the blood lead range studied, followed by women, then adult males.

Figure 1-25 presents dose-population response data for urinary ALA exceeding two levels (at mean + 1 S.D. and mean + 2 S.D.), as calculated by EPA from the data of Azar et al. (1975). The percentages of the study populations exceeding the corresponding cut-off levels as calculated by EPA for the Azar data are set forth in Table 1-18. It should be noted that the measurement of ALA in the Azar et al. study did not account for aminoacetone, which may influence the results observed at the lowest blood lead levels.

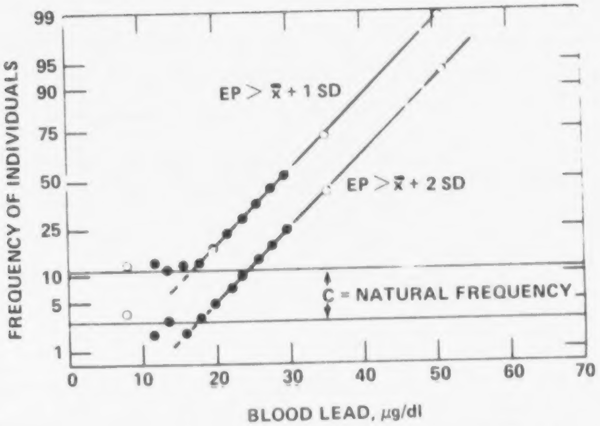

Figure 1-23. Dose-response for elevation of EP as a function of blood lead level using probit analysis. Geometric mean plus 1 S.D. = 33 μg/dl; geometric mean plus 2 S.D. = 53 μg/dl.

Source: Piomelli et al. (1982).

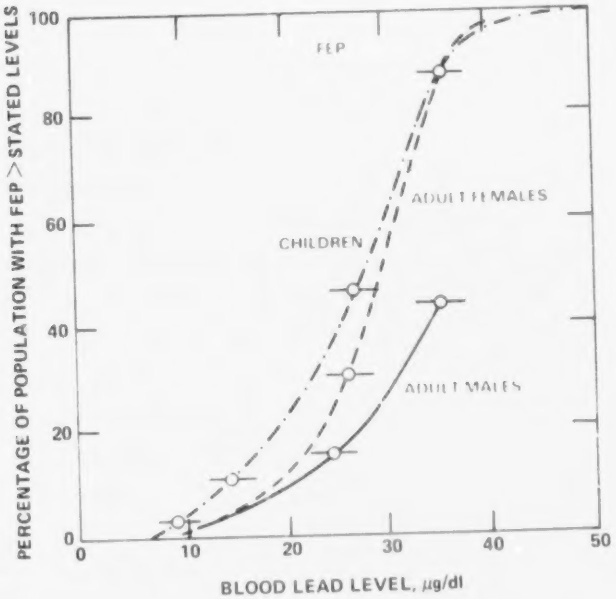

Figure 1-24. Dose-response curve for FEP as a function of blood lead level in subpopulations.

Source: Roels et al. (1976).

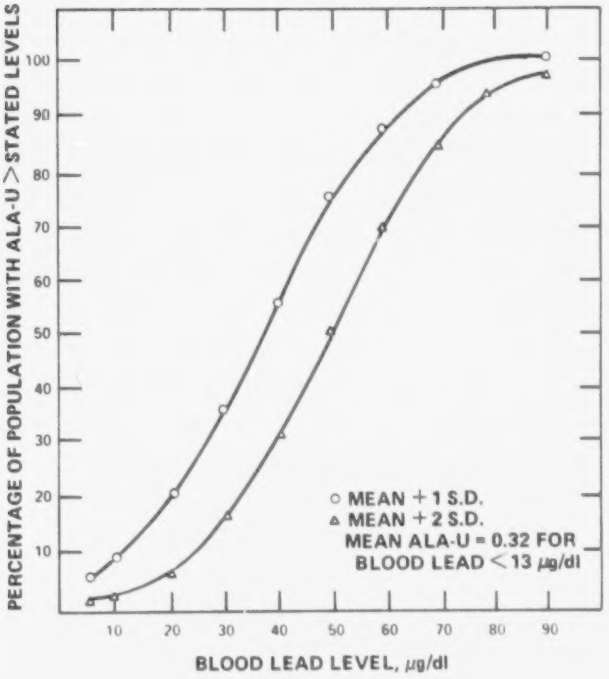

Figure 1-25. EPA-calculated dose-response curve for ALA-U.

Source: Azar et al. (1975).

TABLE 1-18. EPA-ESTIMATED PERCENTAGE OF SUBJECTS WITH ALA-U EXCEEDING LIMITS FOR VARIOUS BLOOD LEAD LEVELS

Blood lead levels, μg/dl	Azar et al. (1975), percent population
10	2
20	6
30	16
40	31
50	50
60	69
70	84

1.13.6 Populations at Risk

Population at risk is a segment of a defined population exhibiting characteristics associated with significantly higher probability of developing a condition, illness, or other abnormal status. This high risk may result from either (1) greater inherent susceptibility or (2) exposure situations peculiar to that group. What is meant by inherent susceptibility is a host characteristic or status that predisposes the host to a greater risk of heightened response to an external stimulus or agent.

In regard to lead, three such populations are definable: they are preschool age children (≤6 years old), especially those living in urban settings, pregnant women, and white males aged 40-59, although the evidence concerning this latter group is much more limited than that for the other two. Children are such a population for both of the reasons stated above, whereas pregnant women are at risk primarily due to the inherent susceptibility of the conceptus. Also, for reasons not as yet fully understood, the limited information available indicates that middle-aged white males appear to be differentially more at risk for manifesting elevations in blood pressure in response to lead exposure (see the Addendum to this document for a complete discussion of the evidence supporting this).

Children as a Population at Risk. Children are developing and growing organisms exhibiting certain differences from adults in terms of basic physiologic mechanisms, capability of coping with physiologic stress, and their relative metabolism of lead. Also, the behavior of children frequently places them in different relationship to sources of lead in the environment, thereby enhancing the opportunity for them to absorb lead. Furthermore, the occurrence of excessive exposure often is not realized until serious harm is done. Young children do not readily communicate a medical history of lead exposure, the early signs of such being common to so many other disease states that lead is frequently not recognized early on as a possible etiological factor contributing to the manifestation of other symptoms.

Discussion of the physiological vulnerability of the young must address two discrete areas. Not only should the basic physiological differences be considered that one would expect to predispose children to a heightened vulnerability to lead, but also the actual clinical evidence must be considered that shows such vulnerability does indeed exist.

In Chapter 10 and Section 1.13.2 above, differences in relative exposure to lead and body handling of lead for children versus adults are noted. The significant elements of difference include the following: (1) greater intake of lead by infants and young children into the respiratory and gastrointestinal (GI) tracts on a body weight basis compared to adults; (2) greater absorption and retention rates of lead in children; (3) much greater prevalence of nutrient deficiency in the case of nutrients which affect lead absorption rates from the GI tract; (4) differences in certain habits, i.e., normal hand-to-mouth activity as well as pica resulting in the transfer of lead-contaminated dust and dirt to the GI tract; (5) differences in the efficiency of lead sequestration in the bones of children, such that not only is less of the body burden of lead in bone at any given time, but the amount present may be relatively more labile. Additional information discussed in Chapter 12 suggests that the blood-brain barrier in children is less developed, posing the risk for greater entry of lead into the nervous system.

Hematological and neurological effects in children have been demonstrated to have lower thresholds in terms of blood lead levels than in adults. Similarly, reduced hemoglobin production and EP accumulation occur at relatively lower exposure levels in children than in adults, as indexed by blood lead thresholds. With reference to neurologic effects, the onset of encephalopathy and other injury to the nervous system appears to vary both regarding likely lower thresholds in children for some effects and in the typical pattern of neurologic effects presented, e.g., in encephalopathy or other CNS deficits being more common in children versus peripheral neuropathy being more often seen in adults. Not only are the effects more acute in children than in adults, but also the neurologic sequelae are usually much more severe in children.

The dietary habits of children as well as the diets themselves differ markedly from adults and, as a result, place children in a different relationship to several sources of lead. The dominance of canned milk and processed baby food in the diet of many young children is an important factor in assessing their exposure to lead, since both those foodstuffs have been shown to contain higher amounts of lead than components of the adult diet. The importance of these lead sources is not their relationship to airborne lead directly but, rather, their role in providing a higher baseline lead burden to which the airborne contribution is added.

Children ordinarily undergo a stage of development in which they exhibit normal mouthing behavior, as manifested, for example, in the form of thumbsucking. At this time they are at risk for picking up lead-contaminated soil and dust on their hands and hence into their mouths where it can be absorbed.

There is, however, an abnormal extension of mouthing behavior, called pica, which occurs in some children. Although diagnosis of this is difficult, children who exhibit this trait have been shown to purposefully eat nonfood items. Much of the lead poisoning due to lead-based paint is known to occur because children actively ingest chips of leaded paint.

Pregnant Women and the Conceptus as a Population at Risk. There are some rather inconculsive data indicating that women may in general be at somewhat higher risk to lead than men. However, pregnant women and their concepti as a subgroup are demonstrably at higher risk. It should be noted that, in fact, it really is not the pregnant woman *per se* who is at greatest risk but, rather, the unborn child she is carrying. Because of obstetric complications, however, the mother herself can also be at somewhat greater risk at the time of delivery of her child. With reference to maternal complication at delivery, information in the literature suggests that the incidence of preterm delivery and premature membrane rupture relates to maternal blood lead level. Further study of this relationship as well as studies relating to discrete health effects in the newborn are needed.

Vulnerability of the developing fetus to lead exposure arising from transplacental transfer of maternal lead is discussed in Chapter 10. This process starts at the end of the first trimester. Umbilical cord blood studies involving mother-infant pairs have repeatedly shown a correlation between maternal and fetal blood lead levels.

Further suggestive evidence, cited in Chapter 12, has been advanced for prenatal lead exposures of fetuses possibly leading to later higher instances of postnatal mental retardation among the affected offspring. The available data are insufficient to state with any certainty that such effects occur or to determine with any precision what levels of lead exposure might be required prior to or during pregnancy in order to produce such effects.

Studies have demonstrated that women in general, like children, tend to show a heightened response of erythorcyte protoporphyrin levels upon exposure to lead. The exact reason for this heightened response is not known but may relate to endocrine differences between men and women.

Middle-Aged White Males (Aged 40-59) as a Population at Risk

Recently-emerging epidemiological evidence indicates that increased blood pressure is associated with blood lead concentrations ranging from $\geq$30-40 µg/dl down to blood lead levels possibly as low as 7 µg/dl. This relationship appears to be particularly significant for middle-aged white males (aged 40-59), although a considerable degree of uncertainty surrounds the statistical analyses of the studies giving rise to this conclusion. A detailed critique of the various analyses which have been performed on the available epidemiological studies concerning the blood lead/blood pressure relationship, as well as a discussion of the plausible biological mechanisms underlying this relationship, are presented in Section 1 of the Addendum to this document.

The specific magnitudes of risk obtained for serious cardiovascular outcomes in relation to lead exposure, estimated on the basis of lead-induced blood pressure increase, depends crucially upon the size of the coefficients estimated for the blood lead/blood pressure association. Given the fact that significant uncertainty exists in regard to the most appropriate blood-lead blood-pressure coefficient(s) to use in attempting to project serious cardiovascular outcomes, the further analysis of additional large-scale epidemiological data sets will be necessary in order to resolve more precisely the quantitative relationship(s) between blood lead and blood pressure. It is possible, however, to identify at this time the population subgroup of middle-aged white males (aged 40-59) as being yet another group at general risk in terms of manifesting notable health effects in response to lead exposure.

Description of the United States Population in Relation to Potential Lead Exposure Risk. In this section, estimates are provided of the number of individuals in those segments of the population which have been defined as being potentially at greatest risk for lead exposures. These segments include preschool children (up to 6 years of age), especially those living in urban settings, women of child-bearing age (defined here as ages 15-44), and white males, aged 40-59. These data, which are presented below in Table 1-19, were obtained from a provisional report by the U.S. Bureau of the Census (1984). Data from the 1980 Census indicates that approximately 61 percent of the populace lives in urban areas (defined as central cities and urban fringe). Assuming that the 61 percent estimate for urban residents also applies to children of preschool age, then approximately 15,495,000 children of the total listed in Table 1-19 would be expected to be at greater risk by virtue of higher lead exposures generally associated with their living in urban versus non-urban settings. (NOTE: The age distribution of the percentage of urban residents may vary between SMSA's.)

The risk encountered with exposure to lead may be compounded by nutritional deficits (see Chapter 10). The most commonly seen deficit is iron deficiency, especially in young children less than 5 years of age (Mahaffey and Michaelson, 1980). Data available from the National Center for Health Statistics for 1976-1980 (Fulwood et al., 1982) indicate that from 8 to 22 percent of children aged 3-5 may exhibit iron deficiency, depending upon whether this condition is defined as serum iron concentration (<40 µg/dl) or as transferrin saturation (<16 percent), respectively. Hence, of the 22,029,000 children ≦5 years of age (Table 1-19), as many as 4,846,000 would be expected to be at increased risk, depending on their exposure to lead, due to iron deficiency.

As pointed out in the preceding section, the risk to pregnant women is mainly due to risk to the conceptus. By dividing the total number of women of child-bearing age in 1984 (56,602,000) into the total number of live births in 1984 (3,697,000; National Center for Health Statistics, 1985), it may be seen that approximately 7 percent of this segment of the population may be at increased risk at any given time.

As for white males, aged 40-59, defined as being at risk notably for increased blood pressure in association with elevated blood lead levels, approximately 20 million individuals can be estimated to be at potential risk based on the 1980 Census data.

TABLE 1-19. PROVISIONAL ESTIMATE OF THE NUMBER OF INDIVIDUALS IN URBAN AND RURAL POPULATION SEGMENTS AT GREATEST POTENTIAL RISK TO LEAD EXPOSURE

Population segment	Actual age, (yr)	Total number in U.S. population (1984)	Urban population*
Preschool children	0-4	18,453,000	11,256,000
	5	3,576,000	2,181,000
	6	3,374,000	2,058,000
Total		25,403,000	15,495,000
Women of child-bearing age	15-19	9,019,000	5,502,000
	20-24	10,481,000	6,393,000
	25-29	10,869,000	6,630,000
	30-34	10,014,000	6,109,000
	35-39	9,040,000	5,514,000
	40-44	7,179,000	4,379,000
Total		56,602,000	34,527,000
White males	40-44	6,064,000	3,699,000
	45-49	4,960,000	3,026,000
	50-54	4,600,000	2,806,000
	55-59	4,760,000	2,904,000
Total		20,384,000	12,435,000

*An urban/total ratio of 0.61 was used for all age groups. "Urban" includes central city and urban fringe populations (U.S. Bureau of the Census, 1983).

Source: U.S. Bureau of the Census (1984), Table 6.

1.13.7 Summary and Conclusions

Among the most significant pieces of information and conclusions that emerge from the present human health risk evaluation are the following:

(1) Anthropogenic activity has clearly led to vast increases of lead input into those environmental compartments which serve as media (e.g., air, water, food, dust, and soil, etc.) by which significant human exposure to lead occurs. Current blood levels of populations in industrialized societies best reflect this impact of man's activities, such lead levels being many fold higher than blood lead levels found in contemporary populations remote from industrial activities.

(2) Emission of lead into the atmosphere, especially through leaded gasoline combustion, is of major significance in terms of both the movement of lead to other environmental compartments and the relative impact of such emissions on the internal lead burdens in industrialized human populations. By means of both mathematical modeling of available clinical/epidemiological data by EPA and the isotopic tracing of lead from gasoline to the atmosphere to human blood of exposed populations, the size of atmospheric lead contribution to human blood lead levels in industrialized areas is estimated to be 25-50 percent.

(3) Given this magnitude of relative contribution to human external and internal exposure, reduction in levels of atmospheric lead would then result in significant widespread reductions in levels of lead in human blood (an outcome which is supported by careful analysis of the NHANES II study data). Reduction of lead in food (added in the course of harvesting, transport, and processing) would also be expected to produce significant widespread reductions in human blood lead levels in the United States, as would efforts to decrease the numbers of American children residing in housing with interior or exterior lead-based paint.

(4) A number of adverse effects in humans and other species are clearly associated with lead exposure and, from an historical perspective, the observed "thresholds" for these various effects (particularly neurological and heme biosynthesis effects) continue to decline as more sophisticated experimental and clinical measures are employed to detect more subtle, but still significant effects. These include significant alterations in normal physiological functions at blood lead levels markedly below the currently accepted 25 µg/dl "maximum safe level" for pediatric exposures.

(5) Preceding chapters of this document demonstrate that young children are at greatest risk for experiencing lead-induced health effects, particularly in the urbanized, low income segments of this pediatric population. A second group at increased risk is pregnant women, because of exposure of the fetus to lead in the absence of any effective biological (e.g., placental) barrier during gestation. A third group at increased risk would appear to be white males, aged 40-59, in that blood pressure elevations appear to be significantly correlated with elevations in blood lead level in this group.

(6) Dose-population response information for heme synthesis effects, coupled with information from various blood lead surveys, e.g., the NHANES II study, indicate that large numbers of American children (especially low-income, urban dwellers) have blood lead levels sufficiently high (in excess of 15-20 μg/dl) that they are clearly at risk for deranged heme synthesis and, possibly, other health effects of growing concern as lead's role as a general systemic toxicant becomes more fully understood.

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LEAD EFFECTS ON CARDIOVASCULAR FUNCTION, EARLY DEVELOPMENT, AND STATURE: AN ADDENDUM TO U.S. EPA *AIR QUALITY CRITERIA FOR LEAD* (1986)

September, 1986

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REVIEWERS

Drafts of this Addendum were circulated for public comment and for review by the Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board (SAB). Members of the CASAC Subcommittee on Lead listed in the front matter of the main 1986 document *Air Quality Criteria for Lead* also reviewed the present Addendum to the 1986 document.

1. INTRODUCTION

The 1977 EPA criteria document, Air Quality Criteria for Lead (EPA-600/8-77-071) has been updated and revised pursuant to Sections 108-109 of the Clean Air Act, as amended, 42 U.S.C. 7408 and 7409. As part of this process, EPA released two external review drafts of the revised Criteria Document, Air Quality Criteria for Lead (EPA-600/8-82-028A&B), which were made available both for public comment and peer review by the Clean Air Scientific Advisory Committee (CASAC) of the Agency's Science Advisory Board. A final version of the updated criteria document incorporating revisions made in response to public comments and CASAC review of earlier drafts has been completed (U.S. EPA, 1986), and will be used as a basis for review and, as appropriate, revision of the National Ambient Air Quality Standard (NAAQS) for lead.

Not fully evaluated in the revised Criteria Document, however, are recently published papers concerning: (1) the relationship between blood lead levels and cardiovascular effects; and (2) lead exposure effects on early development and stature. The present Addendum to the revised document, Air Quality Criteria for Lead (U.S. EPA, 1986), evaluates newly published information concerning both of these topics.

2. LEAD EFFECTS ON THE CARDIOVASCULAR SYSTEM

Lead has long been reported to be associated with cardiovascular effects, in both human adults and children. This section assesses pertinent literature on the subject, including: (1) studies of cardiotoxic effects in overtly lead-intoxicated individuals; (2) epidemiologic studies of associations between lead exposure and increased blood pressure, including observations for non-overtly intoxicated subjects; (3) toxicologic data providing experimental evidence for lead-induced cardiovascular effects in animals and (4) information on possible mechanisms of action underlying lead's cardiovascular effects.

2.1 Cardiotoxic Effects in Overtly Lead-Intoxicated Human Adults and Children

Structural and functional changes suggestive of lead-induced cardiac abnormalities have been described for both adults and children, always in individuals with clinical signs of overt intoxication. For instance, in reviewing five fatal cases of lead poisoning in young children, Kline (1960) noted that degenerative changes in heart muscle were reported to be the proximate cause of death; it was not possible, however, to establish that the observed changes were directly due to lead intoxication per se. In another study, Kósmider and Petelenz (1962) found that 66 percent of a group of adults over 46 years old with chronic lead poisoning had electrocardiographic abnormalities, a rate four times the adjusted normal rate for that age group. Additional evidence for a possible etiological role of higher level lead exposure in the induction of disturbances in cardiac function derives from observations of the disappearance of electrocardiographic abnormalities following chelation therapy in the treatment of many cases of lead encephalopathy (Myerson and Eisenhauer, 1963; Freeman, 1965; Silver and Rodriguez-Torres, 1968). The latter investigators, for example, noted abnormal electrocardiograms in 21 (70 percent) of 30 overtly lead-intoxicated children prior to chelation therapy, but abnormal electrocardiograms remained for only four (13 percent) after such therapy (Silver and Rodriguez-Torres, 1968). None of the above studies provide definitive evidence that lead induced the observed cardiotoxic effects, although they are highly suggestive of an etiological role of lead in producing such effects. Some recently reported human autopsy study results (Voors et al., 1982) showing associations between heart-disease mortality and elevated aortic lead levels also point toward possible involvement of lead in cardiotoxic disease processes.

2.2 Epidemiologic Studies of Blood Lead/Blood Pressure Relationships

Hypertension or, more broadly, increased blood pressure represents the single main type of cardiovascular effect long studied as possibly being associated with excessive lead exposure. As long ago as 1886, Lorimer reported that high blood lead levels increased the risk of hypertension. However, from then until recently, relatively mixed and often apparently contradictory results have been reported concerning lead-hypertension effects. That is, numerous investigators reported significant associations between hypertension and lead poisoning (Oliver, 1891; Legge, 1901; Vigdortchik, 1935; Emmerson, 1963; Dingwall-Fordyce and Lane, 1963; Richet et al., 1966; Morgan, 1976; Beevers, et al., 1976), whereas other studies failed to find a statistically significant association at $p < 0.05$ (Belknap, 1936; Fouts and Page, 1942; Mayers, 1947; Brieger and Rieders, 1959; Cramer and Dahlberg, 1966; Malcolm, 1971; Ramirez-Cervantes et al., 1978). The potential contribution of lead to hypertension was difficult to resolve based on the results of such studies, due to many methodological differences and problems (e.g., lack of comparable definitions of lead exposure and prospective control populations, variations in how hypertension was defined or measured as the key health endpoint, etc.).

In contrast to the generally confusing array of results derived from the above studies, a more consistent pattern of results has begun to emerge from recent investigations of relationships between lead exposures and increases in blood pressure or hypertension. A variety of study designs or approaches have been used in the recent studies and relationships examined between a wide range of blood lead levels and increases in blood pressure in various clinically-defined, occupationally-exposed, or general population groups.

In a case-control pilot study of clinically-defined groups, Khera et al. (1980) measured lead and cadmium levels in single-draw blood and urine samples from 50 patients being seen at General Hospital, Birmingham, UK for moderate or severe cardiac condition and/or hypertension and from 75 other patients with no known cardiovascular symptoms. After excluding small numbers of women, non-Caucasians, and patients <30 yrs old, data for the remaining 38 male cardiovascular patients were compared to those for 48 matched normotensive controls. Urine metal levels were highly variable (24 hr samples being needed to overcome diurnal variations), but average levels were higher in cardiovascular (PbU $\bar{x}$ = 0.34 μ mol/l) than normotensive (PbU $\bar{x}$ = 0.27 μ mol/l) patients. The cardiovascular patients also had higher blood lead levels ($\bar{x}$ = 2.17, range 0.43-4.0 μ mol/l) than the normotensives ($\bar{x}$ = 1.4, range 0.58 - 2.2 μ mol/l).* Hypertensive patients (N = 13) had somewhat higher mean blood lead levels than other cardiovascular disease patients (N = 25), and both of these groups had distinctly higher PbB values than the 48 normotensive subjects. Furthermore, blood lead levels were consistently notably higher for cardiovascular patients than normotensive subjects when compared within 4 different age groups (i.e., 30-39, 40-49, 50-59, and >60 yrs). The authors noted that smoking habits were not determined well enough to allow for firm conclusions, but overall results showed little change for smoking and lead levels, whereas cadmium levels were distinctly higher in smokers and ex-smokers. These descriptive pilot study results, not formally analyzed for statistical significance, qualitatively suggest higher lead burdens in cardiovascular disease (especially hypertensive) patients than in matched normotensive control subjects, but do not permit any firm conclusions as to whether lead causally contributed to the etiology of the cardiovascular disease states.

Batuman et al. (1983), in another study of clinically-defined groups, evaluated chelatable lead burdens in 48 male patients seen for essential hypertension at a Veterens Administration Hospital in New Jersey. Patients (N = 27) having essential hypertension with reduced renal function (serum creatinine level >1.5 mg/dl) had significantly ($p < 0.001$) larger amounts of chelatable lead ($\bar{x}$ = 860 ± 101 μg Pb/3 days) in their urine after EDTA challenge than did 21 essential hypertension patients without renal disease ($\bar{x}$ = 340 ± 39 μg Pb/3 days). EDTA test urine lead levels for the latter normal renal function hypertension patients did not differ significantly from 22 control patients with known renal failure etiologies. The authors interpreted their study as suggesting a possible etiological role of lead in the renal disease of some patients designated as having essential hypertension (in this case patients not currently occupationally exposed to lead but having lead burdens indicative of likely past high exposures). The fact that control patients with known non-gout etiology did not have elevated lead levels, as well as evidence from other studies (Wedeen, 1982; Wedeen et al., 1985; Weeden, 1986), indicate that renal failure associated with hypertension did not result in impaired renal excretion of Pb and consequent increased accumulation of greater lead body stores as a possible explanation for the observed results.

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*Note that 1 μ mole/l ≅ 20.7 μg/dl blood lead. Thus, the mean blood lead levels ($\bar{x}$) ≅ 44.9 μg/dl for the cardiovascular patients and $\bar{x}$ ≅ 29.0 μg/dl for the normotensive subjects.

Another approach employed in recently reported studies of blood-lead blood-pressure relationships has been the study of groups of workers with varying levels of lead exposure. As part of the Glostrup study in Denmark, Kirkby and Gyntelberg (1985) evaluated the coronary risk profiles for 96 heavily-exposed lead smelter workers employed between 9 and 45 years in comparison to that of a non-occupationally exposed reference group matched with respect to age, sex, height, weight, socioeconomic status, and alcohol/tobacco consumption. The lead workers had mean blood lead (PbB $\bar{x}$) levels of 51 ± 16 (S.D.) µg/dl, while the mean for the referent control group was 11 ± 3 (S.D.) µg/dl. Blood pressure was taken both with the subject in the supine position (with a random zero sphygmomanometer) and in the sitting position (with a more usual mercury sphygmomanometer); systolic ankle and arm blood pressure levels were also measured by the Doppler ultrasound technique; resting electrocardiograms with nine leads were recorded and coded according to the Minnesota Code by a trained expert; and participants were administered an extensive questionnaire including questions on subjective symptoms, chest pain, alcohol and tobacco usage, cardiovascular disease among relatives and other pertinent information. Table A-1 shows the results obtained for the lead workers and the referent group for body weight, blood pressure measurements, and lipids.

Statistical analyses of results were carried out by Mann-Whitney and chi-square tests of significance for differences between the comparison groups. No significant differences were obtained for alcohol consumption, smoking habits, or other life-style factors; nor was body weight significantly different between the groups. In regard to blood pressure determined by sphygmomanometer, no significant differences were obtained (at $p < 0.05$) for systolic pressure in either the supine or sitting positions, whereas diastolic pressure was significantly elevated for lead workers in both the supine (+4 mm Hg) and sitting (+5 mm Hg) positions. Systolic pressure monitored by more sensitive ultrasound techniques was, however, significantly elevated in the left (but not right) arm and the dorsal arteries of both right and left feet. As for other cardiovascular risk factors, a significantly ($p < 0.01$) higher percentage (20 percent) of lead workers had ischemic electrocardiographic (ECG) changes than

Table A-1. Body weight, blood pressure, and lipid values of lead workers and referents. (NS = not significant)

	Lead Employees		Referents		Level of significance
	Mean	SD	Mean	SD	
Body weight (kg)	78.6	11.9	76.0	11.2	NS[a]
Blood pressure (mm Hg)[b]					
Sitting position					
Systolic	135	21	133	20	NS
Diastolic	86	12	82	11	0.04
Supine position					
Systolic	135	18	129	18	NS
Diastolic	83	12	78	12	0.005
Ultrasound systolic pressure					
Right arm	135	18	133	17	NS
Left arm	144	19	135	19	0.03
Right dorsal artery of foot	165	28	154	22	0.05
Left dorsal artery of foot	164	27	155	23	0.03
Lipids					
Total cholesterol (mg%)	247.1	50.1	247.1	51.6	NS
Triglycerides (mmol/l)	1.24	0.87	1.33	1.33	NS
High-density lipoprotein cholesterol (mg%)	50.5	9.5	54.9	11.6	0.004

[a] NS = not significant at $p < 0.05$.

[b] 1 mm Hg = 0.133 kPa.

Source: Kirkby and Gyntelberg (1985)

did referent control subjects (6 percent); but no significant differences were observed for percentages having angina pectoris or intermittent claudication or in regard to serum lipid levels (except for lower mean high-density lipoprotein cholesterol for the lead workers). The lead workers with ECG changes had significantly higher blood pressure levels than referents with ECG changes for both systolic and diastolic measures in both supine and sitting positions ($p < 0.05$ for all four comparisons). The authors concluded that long-term lead workers in this study have higher coronary risk profiles than a comparable referent group and that these findings may indicate a greater risk for major cardiovascular diseases, such as myocardial infarction or stroke.

Overall, the Kirkby and Gyntelberg (1985) study appears to have been carefully conducted and to have yielded results with a considerable degree of internal consistency in regard to blood pressure determinations obtained by several different procedures. Also, these findings do point toward higher cardiovascular risk for lead smelter workers, most clearly in terms of increased blood pressure. The evidence for increased blood pressure and other cardiovascular risk factors being specifically due to lead exposure is less clear, given that a correlational analysis between blood lead levels, zinc protoporphyrin, and blood pressure levels was reported as yielding no statistically significant correlations and the workers were exposed to other toxic agents in the workplace (e.g., antimony, smoke and dust) that might exert cardiovascular effects. On the other hand, neither did other factors with known association with high blood pressure (e.g., body weight, smoking, etc.) explain the differences observed between the lead worker and referent control groups, and insufficient description of the correlational analysis was provided to allow evaluation of its soundness. If lead exposure did contribute to the observed higher blood pressure values seen in the lead workers, the magnitude of the effect did not appear to be very large, e.g., a difference of 4-5 mm Hg diastolic increase associated with a difference in mean blood lead level of ~40 µg/dl or 0.1-0.125 mm Hg per µg/dl blood lead.

Another recently reported study (deKort et al., 1986) examined blood pressure in occupationally exposed workers (from a plant processing lead and cadmium compounds used as stabilizers in the plastic industry) in relation to a control group of workers (from a plant where insulation materials are produced). Data were included only for workers employed longer than 1 yr in each plant and not being treated for hypertension. Blood lead (PbB), blood cadmium (CdB) and urine cadmium (CdU) were determined by atomic absorption (AA) spectrophotometry, blood pressure by random-zero sphygmomanometer, and information concerning medical history, medications, smoking habits, and other personal characteristics by questionnaire. Chi-square and two-tailed Student's t-tests were used to test for significant differences between the comparison groups. Data were included in the analyses for 53 male workers in the lead-exposed group and for 52 persons for the control group. The former were, on an average, 3.9 years older ($p < 0.05$) and had been at work 3.9 years longer than control subjects, but smoking habits were comparable. Blood lead values for the exposed group averaged 47.4 µg/dl (ranging up to 60-70 µg/dl), whereas the control group averaged 8.1 µg/dl (none exceeding 20 µg/dl). Statistical analyses showed blood pressure levels to be positively correlated with PbB and CdU but not CdB. The correlation for systolic pressure and PbB remained significant after controlling for confounding variables. The authors concluded that a positive relationship existed between blood lead and blood pressure at levels near or below 60-70 µg/dl.

Besides the above studies of occupationally lead-exposed workers, Moreau et al. (1982) reported findings for 431 male civil service employees (aged 24 to 55 yrs) belonging to the Paris police department. For each subject examined during a routine medical visit (during May, 1980 to February, 1981), blood pressure was measured by a mercury apparatus, blood lead levels determined by AA spectrometry, and information on alcohol and tobacco usage obtained by questionnaire. Statistical analyses were carried out, using log PbB values which appeared to be normally distributed. Significant correlations between blood lead and systolic blood pressure were found, even after taking into account age, wine consumption, and tobacco usage. Correcting for body mass (ratio weight/height^2) did not alter the results. A weaker, but significant, association was reported for diastolic pressure in relation to PbB levels. In a letter concerning the same data set, Orssaud et al. (1985) later reported additional analyses in which systolic blood pressure values were adjusted for body mass index, age, and alcohol consumption using an analysis of covariance. The results are summarized in Table A-2, with systolic blood pressure values (both unadjusted and adjusted) grouped in relation to the same blood lead classes used by Pocock et al. (1984), as discussed later.

Table A-2. Systolic blood pressure means in relation to blood lead concentrations.

Blood lead (µmol/l)	Systolic blood pressure		No. of subjects
	Mean (and 2 SE) (mm Hg)	Adjusted mean	
<0.60	127 (3.6)	129	46
0.61-0.89	130 (1.8)	130	212
0.90-1.19	133 (2.4)	132	126
1.20-1.49	139 (4.8)	138	34
1.50-1.79	143 (13.6)	142	7
≥1.80	130 (5.4)	129	6

Source: Orssaud et al. (1985)

Overall, the blood pressure means differ significantly ($p < 0.001$) by blood lead group, increasing consecutively from the first group (<0.60 µmol/l $\cong$ 12.4 µg/dl) to the fourth (1.20 to 1.49 µ mol/l $\cong$ 24.8 to 30.8 µg/dl). The means for the last two groups (>1.50 µ mol/l $\cong$ 31 µg/dl) are based on very small N's and were not viewed by the authors as yielding useful information. The overall correlation between blood lead level and systolic pressure was 0.23 ($p < 0.001$); correlations for the age classes 24 to 34 years (N = 145), 34 to 44 years (N = 143), and 45 to 55 years (N = 142) were 0.29 ($p < 0.001$), 0.20 ($p < 0.05$), and 0.14 (N.S.), respectively. Adjusting for alcohol consumption and body mass index, it was noted, did not alter these results. The authors concluded that blood pressure was related to blood lead values, the correlation being highest in young subjects but decreasing with age. In general, the results are highly suggestive of increases in systolic pressure being associated with blood lead values in adult males across a range of ~12 to 30 µg/dl, the increase not being particularly large (about 9 mm Hg or 0.5 mm Hg per µg/dl blood lead). However, it is not clear as to why tobacco consumption (although measured) was apparently not included in the statistical analyses and to what extent its inclusion would have affected the reported results. Nor is it completely clear as to what results were obtained for diastolic pressure in the analyses reported on later by Orssaud et al. (1985). For example, do the weaker associations for blood lead-diastolic pressure reported by Moreau et al. (1982) become non-significant or no longer evident when adjustments are made for other factors, as evaluated in the analyses reported by Orssaud for systolic pressure results?

More recently, Weiss et al. (1986) examined blood-lead blood-pressure relationships in a longitudinal study of a cohort of 89 Boston, MA policemen. During baseline examination, blood lead determinations were obtained (AA spectrophometry) and three consecutive blood pressure measurements taken, using a random-zero instrument. With the subject seated, systolic blood pressure and fifth phase diastolic pressure were measured on the left arm. Triplicate blood pressure measurements were also taken at years 3, 4, and 5. Multivariate analyses showed that, after correction for previous systolic blood pressure, body mass index, age, and smoking, high blood lead level was a significant predictor of subsequent blood pressure elevation. More specifically, auto-regressive analyses were performed for blood lead and blood pressure data from 70 subjects providing 162 pairs of data (by consecutive examination) for the systolic regression. There was a significant association ($p = 0.036$) between high (≧30 µg/dl) blood lead and subsequent elevation in blood pressure (coefficient = 5.804) but not for low (20 to 29 µg/dl) blood lead (coefficient = 0.224). Similar analyses for 172 pairs of data from 72 subjects for diastolic pressure revealed no significant association between blood lead and diastolic pressure. Further iterative cross-validation analyses (assessing the impact of a few influential data points) improved the relationship between systolic pressure and other independent variables (e.g., body mass index, age, etc.) but did not dramatically alter the relationship with high blood lead (coefficient = 4.467, $p < 0.097$). Overall, the authors concluded that these data suggest a relationship between blood lead levels and systolic (but not diastolic) blood pressure. The stronger association found between lead and systolic pressure than between lead and diastolic pressure is consistent with the observations by Moreau et al. (1982) and Orssaud et al. (1985) for Paris civil servants. However, the latter had generally lower blood lead levels than the high lead group of Boston policemen (≧30 µg/dl) for which Weiss et al. (1986) found significant blood lead-systolic pressure associations.

One other American study, available thus far only in abstract form (Hodgson et al., 1985), evaluated blood-lead blood-pressure relationships in a cohort of lead workers and controls (all white males of similar socioeconomic status). Separate equations were generated for systolic and diastolic blood pressure as dependent variables and blood lead and zinc protoporphyrin levels as independent variables, controlling for age, body mass index, average daily alcohol consumption, smoking, exercise frequency, and an index of lifetime cumulative lead exposure (for lead workers). Overall R^2 ranged from 0.09 to 0.30; no index of lead exposure accounted for more than 2 percent of the total variance; and none of the lead coefficients were significant (even at $p < 0.10$). Unfortunately, insufficient information was reported in the published abstract to allow adequate assessment of important aspects of the study (e.g., size of the study groups, how well matched they were, etc.).

In addition to the above recent studies of clinically-defined populations or specific worker cohorts, Kromhout and Couland (1984) and Kromhout et al. (1985) evaluated a cohort drawn from the more general population. More specifically, data on trace metals and coronary disease risk indicators were collected in 1977 for 152 men (aged 57-67 yrs) in the town of Zutphen, The Netherlands. Blood lead, blood cadmium, serum zinc, and serum copper were determined by AA spectrometry; serum lithium was determined by flame emission spectrometry. Also, the following coronary heart disease risk indicators were measured: total and high density lipoprotein cholesterol, smoking habits, Quetelet index (weight/height^2), and systolic and diastolic blood pressure. A standard protocol and mercury sphygmomanometer was employed by a single internist in obtaining blood pressure readings from the right arm while the subjects were in a supine position. The first reading was taken at the beginning, and the second and third at the end of the medical examination; only the systolic and diastolic (fifth phase) values of the third reading were recorded. Resting heart rate was calculated from an electrocardiogram. Statistical analyses were carried out using SPSS package programs, including calculation of correlation coefficients, ANOVA, and multiple regression analyses. For skewed distribution variables, log transformations were used, but no differences were found between analyses using transformed or untransformed variables. The levels of coronary heart disease risk indicators were generally high in the elderly cohort; and blood lead levels exceeded 30 µg/dl in 8.6 percent and 40 µg/dl in 1.3 percent of the study group. In addition to several significant associations found between the other metals and various risk indicators, blood lead was found to be statistically significantly related to cigarette smoking ($p < 0.03$), but more markedly related to both systolic and diastolic blood pressure. Using multiple regression analyses correcting for age and body mass index, the PbB regression coefficients were reduced from 0.24 ($p < 0.01$) to 0.21 ($p < 0.01$) for systolic pressure and from 0.18 ($p < 0.05$) to 0.15 ($p < 0.05$) for diastolic. However, in testing the stability of the results by excluding the highest blood lead (52.5 µg/dl) subject with hypertension (218/138 mm Hg), a borderline significant correlation was found between blood lead and systolic pressure, whereas the blood lead-diastolic pressure coefficient became nonsignificant. Neither blood lead coefficient for systolic or diastolic pressure was significant after multiple regression analyses were conducted that include other determinants (e.g., age and body mass index) in the model when the data for the same highest-lead individual was excluded; but the coefficients between blood pressure and age or body mass index were unaffected by his exclusion. The authors concluded that blood lead is probably a less important determinant of blood pressure than age or body mass index.

The above recent studies provide generally consistent evidence of increased blood pressure being associated with elevated lead body burdens in adults, especially as indexed by blood lead levels in various cohorts of working men. None of the individual studies provide definitive evidence establishing causal relationships between lead exposure and increased blood pressure. Nevertheless, they collectively provide considerable qualitative evidence indicative of significant associations between blood lead and blood pressure levels. Particularly striking are the distinct dose-response relationship seen for systolic pressure (correcting for age, body mass, etc.) by Moreau et al. and the findings of significant associations between blood lead and systolic pressure after extensive and conservative statistical analyses by Weiss et al. However, estimates of quantitative relationships between blood lead levels and blood pressure increases derived from such study results are subject to much uncertainty, given the relatively small sample sizes and limited population groups studied. Two larger-scale recent studies of general population groups, reviewed next, provide better bases for estimation of quantitative blood-lead blood-pressure relationships.

In one such recent study, Pocock et al. (1984) evaluated relationships between blood lead concentrations, hypertension, and renal function indicators in a clinical survey of 7735 middle-aged men (aged 40-49) from 24 British towns. Each man's blood pressure was measured while seated twice in succession by means of a London School of Hygiene sphygmomanometer. Diastolic pressure was recorded at phase V disappearance of sounds. The mean of the two readings of blood pressure was adjusted for observed variation within each town to correct for any differences among three observers. Results for 7371 men included in data analyses indicated correlation coefficients of $r = +0.03$ and $r = +0.01$ for associations between systolic and diastolic blood pressure, respectively, and blood lead levels. The systolic blood pressure correlation, though small in magnitude, was nevertheless statistically significant at $p < 0.01$. However, analyses of covariance using data for men categorized according to blood lead concentrations only suggested increases in blood pressure at lower blood lead levels; no further significant increments in blood pressure were observed at higher blood lead levels either before or after adjustment for factors such as age, town, body mass index, alcohol consumption, social class, and observer (see Figure A-1). Evaluation of prevalence of hypertension defined as systolic blood pressure over 160 mm Hg revealed no significant overall trend; but of those men with blood lead levels over 37 µg/dl, a larger proportion (30 percent) had hypertension when compared with the proportion (21 percent) for all other

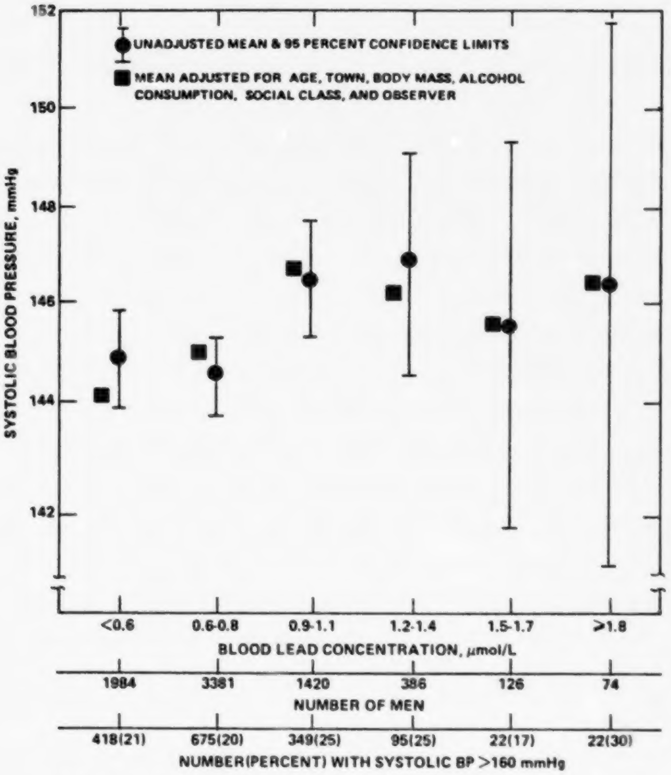

Figure A-1. Systolic blood pressure for 7,371 middle-aged men categorized according to blood lead concentration.
Conversion: SI to customary units -- Lead: 1 µmol/L≅20.7 µg/100 ml.

Source: Pocock et al. (1984).

men combined (p =0.08). Similar results were obtained for diastolic hypertension defined as >100 mmHg, i.e., a greater proportion (15 percent) of men with blood lead levels over 37 µg/dl had diastolic hypertension in comparison with the proportion (9 percent) for all other men (p =0.07). Pocock et al. (1984) interpreted their findings as being suggestive of increased hypertension at blood lead levels over 37 µg/dl, but not at lower concentrations typically found in British men. However, more recent analyses reported by Pocock et al. (1985) for the same data indicate highly statistically significant associations between both systolic (p =0.003) and diastolic (p <0.001) blood pressure and blood lead levels, when adjustments are made for variation due to site (town) in multiple regression analyses. The regression coefficients for log blood lead versus systolic and diastolic pressure were +2.089 and +1.809, respectively, when adjusted for town as well as body mass, age, alcohol, smoking, social class and observer. Noting the small magnitude of the association observed and the difficulty in adjusting for all potentially relevant confounders, Pocock et al (1985) cautioned against prematurely concluding that elevated body lead burden has a causal influence on blood pressure.

Relationships between blood lead and blood pressure among American adults have also been recently evaluated in another large-scale study, as reported by Harlan et al. (1985), Pirkle et al. (1985), Landis and Flegal (1986), and Schwartz (1985a,b; 1986a,b). These analyses were based on evaluation of NHANES II data, which provide careful blood lead and blood pressure measurements on a large-scale sample representative of the U.S. population and considerable information on a wide variety of potentially confounding variables as well. As such, these analyses avoided the problem of selection bias, the healthy-worker effect, workplace exposures to other toxic agents, and problems with appropriate choice of control groups that often confounded or complicated earlier, occupational studies of blood-lead blood-pressure relationships. Three blood pressure readings were recorded for each subject: while seated early in the examination, supine midway in the examination, and seated near the end. First and fifth phase sounds were taken as systolic and diastolic pressures, respectively. The second seated blood pressure was used in statistical analyses, but analyses using the first seated pressure or a mean of the first and second seated pressure yielded similar results. Blood lead values, determined by AA spectrometry, were transformed to log values used in statistical analyses.

Relationships between blood pressure and other variables were evaluated in two ways. First, men and women were stratified into normotensive and hypertensive categories and mean values for relevant variables contrasted across the categories. For ages 21-55 yr, diastolic high blood pressure ($\geq$90 mm Hg) male subjects (N = 475) had significantly ($p < 0.005$) higher PbB levels, body mass index values, and calcium foods than did normotensive male subjects (N = 1,043). Similar results were obtained for aged 21-55 yr diastolic high blood pressure females (N = 263) in comparison to normotensive females (N = 1,316). For ages 56-74 yr subjects, significantly ($p < 0.05$) higher PbB levels were found for female subjects (but not males) defined as having isolated systolic high blood pressure (i.e., systolic $\geq$160 and diastolic <90 mm Hg). Simple correlation analyses and step-wise multiple regression analyses were carried out as a second statistical evaluation approach; PbB values were entered into predictive models for systolic and diastolic pressure as well as several other pertinent variables (such as age, body mass index, etc.) entered sequentially according to greatest magnitude of variance explained for the dependent variable. The simple correlation analyses reported by Harlan et al. (1985) demonstrated statistically significant linear associations ($p < 0.001$) between blood lead concentrations and blood pressure (both systolic and diastolic) among males and females, aged 12 to 74 years. Using multiple regression analyses controlling for a number of other potentially confounding factors, however, the blood-lead blood-pressure cautioned against prematurely concluding that elevated body lead burden has a causal influence on blood pressure.

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Relationships between blood pressure and other variables were evaluated in two ways. First, men and women were stratified into normotensive and hypertensive categories and mean values for relevant variables contrasted across the categories. For ages 21-55 yr, diastolic high blood pressure ($\geq$90 mm Hg) male subjects (N = 475) had significantly ($p < 0.005$) higher PbB levels, body mass index values, and calcium foods than did normotensive male subjects (N = 1,043). Similar results were obtained for aged 21-55 yr diastolic high blood pressure females (N = 263) in comparison to normotensive females (N = 1,316). For ages 56-74 yr subjects, significantly ($p < 0.05$) higher PbB levels were found for female subjects (but not males) defined as having isolated systolic high blood pressure (i.e., systolic $\geq$160 and diastolic <90 mm Hg). Simple correlation analyses and step-wise multiple regression analyses were carried out as a second statistical evaluation approach; PbB values were entered into predictive models for systolic and diastolic pressure as well as several other pertinent variables (such as age, body mass index, etc.) entered sequentially according to greatest magnitude of variance explained for the dependent variable. The simple correlation analyses reported by Harlan et al. (1985) demonstrated statistically significant linear associations ($p < 0.001$) between blood lead concentrations and blood pressure (both systolic and diastolic) among males and females, aged 12 to 74 years. Using multiple regression analyses controlling for a number of other potentially confounding factors, however, the blood-lead blood-pressure associations remained significant for males but not for women after adjusting for the effects of other pertinent variables.

Additional analyses of NHANES II data reported by Pirkle et al. (1985) focussed on white males (aged 40 to 59 years) in order to avoid the effects of collinearity between blood pressure and blood lead concentrations evident at earlier ages and because of less extensive NHANES II data being available for non-whites. In the subgroup studied, Pirkle et al. (1985) found significant associations between blood lead and blood pressure even after including in multiple regression analyses all known factors previously established as being correlated with blood pressure. The relationship also held when tested against every dietary and serologic variable measured in the NHANES II study. Inclusion of both curvilinear transformations and interaction terms altered little the coefficients for blood pressure associations with lead (the strongest relationship was observed between the natural log of blood lead and the blood pressure measures). The regression coefficients for log blood lead versus systolic and diastolic blood pressure were 8.436 and 3.954, respectively. No evident threshold was found below which blood lead level was not significantly related to blood pressure across a range of 7 to 34 µg/dl. In fact, the dose-response relationships characterized by Pirkle et al. (1985) indicate that large initial increments in blood pressure occur at relatively low blood lead levels, followed by leveling off of blood pressure increments at higher blood lead levels. Pirkle et al. (1985) also found lead to be a significant predictor of diastolic blood pressure greater than or equal to 90 mmHg, the criterion blood pressure level now standardly employed in the United States to define hypertension. Additional analyses were performed by Pirkle et al. (1985) to estimate the likely public health implications of their findings concerning blood-lead, blood-pressure relationships. Changes in blood pressure that might result from a specified change in blood lead levels were first estimated. Then coefficients from the Pooling Project and Framingham studies (Pooling Project Research Group, 1978 and McGee and Gordon, 1976, respectively) of cardiovascular disease were used as bases: (1) to estimate the risk for incidence of serious cardiovascular events (myocardial infarction, stroke, or death) as a consequence of lead-induced blood pressure increases and (2) to predict the change in the number of serious outcomes as the result of a 37 percent decrease in blood lead levels for adult white males (aged 40-59 years) observed during the course of the NHANES II survey (1976-1980).

Questions have been raised by Gartside (1985) and E.I. Du Pont de Nemours (1986) regarding the robustness of the findings derived from the analyses of NHANES II data discussed above and as to whether certain time trends in the NHANES II data set may have contributed to (or account for) the reported blood-lead blood-pressure relationships. Gartside reported analyses of HNANES II data which found that the size and level of statistical significance of coefficients obtained varied depending upon specific data aggregations used in analyzing the data. The largest and most significant coefficients for blood lead versus blood pressure were obtained by Gartside for data aggregated by age groups that approximated that of the 40-59 yr male aggregation described by Pirkle et al. (1985), with coefficients for most younger cohorts group aggregated by varying 20 yr age intervals (e.g., 21-40, 22-42 yrs, etc.) or older groups not always being significant at $p < 0.05$. As for the time trend issue, both blood lead and blood pressure declined substantially during the 4-yr NHANES II study and different geographic sites were sampled without revisitation of the same site over the survey period. Thus, variations in the sampling sites over time, coincident with changes in blood lead and/or blood pressure, might contribute to any observed associations between blood lead and blood pressure. E.I. Du Pont de Nemours (1986) reported that multiple regression coefficients decreased in magnitude and some became non-significant at $p < 0.05$ when geographic site was adjusted for in analyses of NHANES II data, including analyses for the male group (aged 12-74) reported on by Harlan et al. (1985) and for males (aged 40-59) reported on by Pirkle et al. (1986). For example, E.I. Du Pont de Nemours reported unpublished reanalyses of NHANES II data confirming significant associations for both aged 12-74 yrs males and 40-59 yr males between log PbB and systolic or diastolic blood pressure unadjusted for geographic site, but smaller coefficients (nonsignificant for diastolic) when geographic site was included in the analysis. However, neither the Gartside nor E.I. Du Pont de Nemours analyses adjusted for all of the variables that were selected for stepwise inclusion in the Harlan et al. (1985) and Pirkle et al. (1986) published analyses by means of a priori decision rules for inclusion of variables having significant associations with blood pressure. Also, other differences existed in regard to specific aspects of the modeling approaches employed, making it extremely difficult to assess clearly the potential impact of variation in selection of age groups and geographic site adjustment on NHANES II analyses results.

In order to more definitively assess the robustness of the Harlan et al. (1985) findings and, also, to evaluate possible time-trend effects confounded by variations in sampling sites, Landis and Flegal (1986) carried out further analyses for NHANES II males, aged 12-74, using a randomization model-based approach to test the statistical significance of the partial correlation between blood lead and diastolic blood pressure, adjusting for age, body mass index, and the 64 NHANES II sampling sites. The resulting analyses confirm that the significant association between blood lead (PbB) and blood pressure (BP) cannot be dismissed as spurious due to concurrent secular trends in the two variables over the NHANES study period. Simple linear and multiple regression coefficients between log PbB and diastolic BP for all males (aged 12-74) were 0.15 and 4.90, respectively; for various groups broken out by age ($\leq$20, 21-39, $\geq$40 yrs) and body mass index levels, the respective coefficients ranged from 0.04 to 0.15 and from 1.29 to 3.55 (predominantly between 2.3 and 3.6), displaying considerable consistency across age-body mass comparison groups. Also, the most stringent or "conservative" approach used to calculate a randomized model statistic controlling for effects due to 64 sampling sites yielded a test statistic of 4.64 (still significant at $P < 0.05$).

In order to address the "site" issue more definitively, Schwartz (1985a,b; 1986a,b) has also carried out a series of additional reanalyses of the NHANES II data. These unpublished analyses confirm that the regression coefficients remain significant for both systolic and diastolic blood pressure when site is included as a variable in multiple regression analyses. Of several different approaches used by Schwartz, the most direct was holding all aspects of the original Pirkle et al. (1985) analyses the same except for the addition of a variable controlling for the 64 geographic sites sampled in NHANES II. Using this approach, the cofficients for log PbB in relation to either diastolic or systolic BP dropped somewhat from those of the original analyses when site was controlled for (i.e., from 8.44 to 5.09 for systolic and from 3.95 to 2.74 for diastolic blood pressure), but the coefficients for each still remained significant at $p < 0.05$. When still other approaches were used to control for site along with variations in other variables included in the analyses, statistically significant results were still consistently obtained both for males aged 40-59 and for males aged 20-74. The results obtained by Schwartz via reanalysis of NHANES II data (unadjusted versus adjusted for geographic site) are presented in Table A-3 in comparison to results reported by E.I. Du Pont de Nemours and in relation to the findings presented by Pocock for British men (also unadjusted versus adjusted for site).

Overall, the analyses of data from the two large-scale general population studies (British Regional Heart Study and U.S. NHANES II Study) discussed above collectively provide highly convincing evidence demonstrating small but statistically significant associations between blood lead levels and increased blood pressure in adult men. The strongest associations appear to exist for males aged 40-59 and for systolic somewhat more so than for diastolic pressure. Virtually all of the analyses revealed positive associations for the 40-59 aged group, which remain or become significant (at $p < 0.05$) when adjustments are made for geographic site. Furthermore, the results of these large-scale studies are consistent with similar findings of statistically significant associations between blood lead levels and blood pressure increases as derived from other recent smaller-scale studies discussed earlier, which also mainly found stronger associations for systolic pressure than for diastolic. None of the observational studies in and of themselves can be stated as definitively establishing causal linkages between lead exposure and increased blood pressure of hypertension. However, the plausibility of the observed associations reflecting causal relationships between lead exposure and blood pressure increases is supported by: (1) the consistency of the significant associations that have now been found by numerous independent investigators for a variety of study populations; and (2) by extensive toxicological data

Table A-3. Coefficients for the Natural Log of Blood Lead Concentration (logPbB) vs. Blood Pressure (BP) in Men With and Without Adjustment for Site Variables

		Coefficient of logPbB vs. BP	
Analysis Performed by	Study Group	Unadjusted for Site	Adjusted for Site
Pocock et al. (1984, 1985)	British Regional Heart Study		
	White males aged 40-59		
	Systolic (n=7371)	1.68**	2.09**
	Diastolic (n=7371)	0.30	1.81***
Schwartz (1985a,b)	NHANES II		
	Males aged 20-74		
	Systolic (n=2254)	5.23***	3.23**
	Diastolic (n=2248)	2.96***	1.39*
E.I. Du Pont de Nemours(1986)	NHANES II		
	Males aged 12-74		
	Systolic (n=2794)	3.43***	1.95*
	Diastolic (n=2789)	2.02***	0.36
Schwartz (1986a,b)	NHANES II		
	White males aged 40-59		
	Systolic (n=543)	8.44**	5.01*
	Diastolic (n=565)	3.95**	2.74*
E.I. Du Pont de Nemours (1986)	NHANES II		
	White males aged 40-59		
	Systolic (n=553)	6.27**	3.46*
	Diastolic (n=575)	4.01**	1.93*

$^{*}p < 0.05$
$^{**}p < 0.01$
$^{***}p < 0.001$

(see below) which clearly demonstrate increases in blood pressure for animal models under well-controlled experimental conditions. The precise mechanisms underlying relationships between lead exposure and increased blood pressure, however, appear to be complex and mathematical models describing the relationships still remain to be more definitively characterized. At present, log PbB-BP models appear to fit best the available data, but linear relationships between blood lead and blood pressure cannot be ruled out at this time. The most appropriate coefficients characterizing PbB-BP relationships also remain to be more precisely determined, although those reported by Landis and Flegal (1986) and those in Table A-3 obtained by analyses adjusting for site appear to be the currently best available and most reasonable estimates of the likely strength of the association (i.e., generally in the range of 2.0-5.0 for log PbB versus systolic and 1.4 to 2.7 for log PbB versus diastolic blood pressure).

Blood lead levels that may be associated with increased blood pressure also remain to be more clearly defined. However, the collective evidence from the above studies points toward moderately elevated blood lead levels (≥30 µg/dl) as being associated most clearly with blood pressure increases, but certain evidence (e.g., the NHANES II data analyses and the Moreau et al. study results) also indicates significant (and apparently stronger) relationships between blood pressure elevations and still lower blood lead levels that range, possibly, to as low as 7 µg/dl.

The quantification of likely consequent risks for serious cardiovascular outcomes, as attempted by Pirkle et al. (1985), also remains to be more precisely characterized. The specific magnitudes of risk obtained for serious cardiovascular outcomes in relation to lead exposure, estimated on the basis of lead-induced blood pressure increases, depend crucially upon: the form of the underlying relationship and size of the coefficients estimated for blood-lead blood-pressure associations; lead exposure levels at which significant elevations in blood pressure occur; and coefficients estimating relationships between blood pressure increases and specific more serious cardiovascular outcomes. As noted above uncertainty still exists regarding the most appropriate model and blood-lead blood-pressure coefficients, which makes it difficult to resolve which specific coefficients should be used in attempting to project more serious cardiovascular outcomes. Similarly, it is difficult to determine appropriate blood lead levels at which any selected coefficients might be appropriately applied in models predicting more serious cardiovascular outcomes. Lastly, the selection of appropriate models and coefficients relating blood pressure increases to more serious outcomes is also fraught with uncertainty. Questions exist regarding the general applicability of coefficients derived from the Pooling Projects and Framingham Study to the men aged 40-59 in the general U.S. population. Further analyses of additional large scale epidemiologic data sets may be necessary in order to determine more precisely quantitative relationships between blood-lead and blood-pressure, and more serious cardiovascular outcomes as well.

The findings discussed here, while pointing toward a likely causal effect of lead in contributing to increased blood pressure need to be placed in broader perspective in relation to other factors involved in the etiology of hypertension. The underlying causes of increased blood pressure or "hypertension" (diastolic blood pressure above 90 mm Hg), which occurs in as many as 25 percent of Americans, are not yet fully delineated (Frolich, 1983; Kaplan, 1983). However, it is very clear that many factors contribute to development of this disease, including hereditary traits, nutritional factors and environmental agents. The relative roles of various dietary and environmental factors in influencing blood pressure and the mechanisms by which they do so are a matter of intense investigative effort and debate (see proceedings of conference "Nutrition and Blood Pressure: Current Status of Dietary Factors and Hypertension," McCarron and Kotchen, 1983). The contribution of lead, compared to many other factors evaluated in various analyses discussed above, appears to be relatively small, usually not accounting for more than 1-2 percent of the variation explained by the models employed when other significant factors are controlled for in the analyses.

2.3 Mechanisms Potentially Underlying Lead-Induced Hypertension Effects

This section discusses plausible biochemical-physiological mechanisms by which lead potentially influences the cardiovascular system to induce increased blood pressure, followed by the evaluation of experimental evidence concerning the contribution of lead exposure to development of hypertension.

Blood pressure is determined by interaction of two factors: cardiac output and total peripheral resistance. An elevation of either or both results in an increase in blood pressure. A subsequent defect in a critical regulatory function (e.g., renal excretory function) may influence central nervous system regulation of blood pressure, leading to a permanent alteration in vascular smooth muscle tone which sustains blood pressure elevation. The primary defect in the pathophysiology of hypertension is thought to be due to alteration in calcium binding to plasma membranes of cells; this change in calcium handling may in turn be dependent upon an alteration in sodium permeability of the membrane (Blaustein, 1977; Rasmussen, 1983; Postnov and Orlov, 1985; Hilton, 1986). This change affects several pathways capable of elevating pressure: one is a direct alteration of the sensitivity of vascular smooth muscle to vasoactive stimuli; another is indirect, via alteration of neuroendocrine input to vascular smooth muscle (including changes in renin secretion rate).

2.3.1 Role of Disturbances in Ion Transport by Plasma Membranes

Many stimuli activate target cells in the mammalian body via changes in ion permeabilities of the plasma membrane, primarily for sodium, potassium, and calcium ions (Carafoli and Penniston, 1985); the change in calcium ion concentration is the primary intracellular signal controlling muscle contractions, hormone secretion, and other diverse activities. Extracellular fluid contains high concentrations of sodium and calcium, while intracellular potassium is high. Intracellular calcium is present in two forms, bound and free ion, with the concentration of the free ion normally about 0.1 μM. These concentration gradients across cell membranes are maintained via the action of membrane-bound energy-requiring or voltage-dependent exchange pumps. For sodium and potassium, the regulatory pump is a sodium/potassium-dependent ATPase which extrudes sodium in exchange for potassium ions and in the process is important in maintaining the cell membrane potential. For calcium, there is a membrane potential-dependent sodium/calcium exchange pump which extrudes one calcium ion in exchange for three sodium ions. In addition, there are calcium ATPase pumps located at cell membranes and at intracellular membrane storage sites (endoplasmic reticulum and mitochondria). As calcium ions move in and out of the cell and in and out of intracellular storage sites, the intracellular free calcium ion ([$Ca^{2}+$]) changes from its resting value to something higher or lower. The ion interacts with several calcium-binding proteins which in turn activate cell contractile or secretory processes.

It has been postulated (Blaustein and Hamlyn, 1983) that sodium pump inhibition by some endogenous factor (thought to be a hormone) could be ultimately causatory for development of both essential and volume-expanded hypertension by affecting vascular tone or resistance. As explained above, the sodium pump maintains and restores the membrane potential subsequent to depolarization events. Decreased sodium pump activity may directly increase membrane permeability to calcium and increase reactivity to calcium-dependent stimuli. Small changes in the distribution of intracellular and extracellular sodium ions affect the membrane potential and cause a much larger decrease in activity of the sodium/calcium exchange pump, resulting in a proportionately much greater elevation in intracellular free calcium ion which in turn increases reactivity to calcium-activated stimuli. Some of the newest antihypertensive therapeutic agents (calcium channel blockers) act to lower intracellular [$Ca^{2}+$] by reducing movement of extracellular calcium into cells, thereby reducing activation of processes requiring such movement. Diuretic drugs may reduce the postulated rise in intracellular sodium concentration related to the decreased Na^{+}/K^{+}-ATPase activity and thereby reduce elevated intracellular calcium by stimulation of the Na/Ca exchange pump.

If lead exposure could be shown to affect sodium transport (which then indirectly alters vascular resistance) or to directly affect vascular resistance (by changing calcium ion permeability or transport), it could contribute to the development of hypertension. In sections previously presented in the revised criteria document (U.S. EPA, 1986), abundant experimental evidence was discussed which indicates that lead affects both; that is, lead inhibits cell membrane-bound Na+/K+-ATPase as well as interferes with normal processes of calcium transport across membranes of various tissue types (see sections 12.2.3 and 12.3.2.2 of U.S. EPA, 1986, for discussion). Highlighted concisely below is evidence that lead acts to alter sodium balance and calcium-activated cell activities of vascular smooth muscle. Changes in either or both of these could be expected to produce changes in blood pressure regulation.

2.3.2 Role of Renin-Angiotensin in Control of Blood Pressure and Fluid Balance; Possible Role of Kallikrein-Kinin in Control of Blood Pressure

One major endogenous factor regulating total peripheral resistance of the vascular smooth muscle is angiotensin II (AII), a small peptide generated in plasma via the action of a renal hormone, renin. Renin is synthesized and stored in juxtaglomerular (JG) cells of the kidney and is released when JG cells receive stimuli indicating a decrease in arterial pressure, as sensed by cardiovascular baroreceptors and transmitted to the central nervous system (CNS) with subsequent activation of efferent β-adrenergic signals to the kidney. Changes in the intracellular calcium ion concentration of the JG cell are thought to be involved in renin release (Churchill, 1985), with an increase in intracellular [$Ca^{2}+$] producing a decrease in renin secretion, while a decrease in intracellular [$Ca^{2}+$] produces an increase in renin release.

Renin is the first enzyme in a series which splits a small peptide, angiotensin I (AI) from angiotensinogen, or renin substrate, a large protein synthesized by liver and found in circulation. AI is converted to AII by angiotensin converting enzyme (ACE), an enzyme found in plasma and lung tissue. AII is degraded to AIII and other breakdown products by various proteolytic enzymes. Renin is cleared from plasma by the liver.

AII acts to increase total peripheral resistance by: (1) direct action on vascular smooth muscle to increase vasoconstriction (it is 10 to 40 times more potent than norepinephrine and acts to elevate cytosolic calcium of vascular smooth muscle to activate the contraction of actin and myosin); and (2) indirectly, by acting on the area postrema of the medulla oblongata to increase the discharge rate of sympathetic neurons (which increases norepinephrine release, decreases its reuptake, and increases vascular sensitivity to norepinephrine).

AII also influences renal function and overall salt and fluid balance in several ways: (1) Renal hemodynamics: glomerular filtration rate is altered by AII-related changes in renal blood flow or indirectly by increased noradrenergic transmission to the kidney resulting from CNS action of AII. (2) Salt and water metabolism: AII-induced changes in renal sympathetic tone alter reabsorption of sodium and potassium; AII stimulates aldosterone secretion which affects sodium and potassium balance; AII may have direct action on the renal tubules to increase electrolyte and water reabsorption. In addition, AII appears to act directly on the CNS to increase thirst.

The renin-angiotensin system thus has a major influence on regulation of blood pressure; for this reason, investigators interested in hypertension have studied the system in detail. Because renal disease may be an important initiating event in subsequent development of hypertension and because lead is an important renal toxicant, some investigative reports of patients with lead intoxication have evaluated blood pressure changes and changes in the renin-angiotensin system. For example, Sandstead et al. (1970) found that dietary sodium restriction produced smaller increases in plasma renin activity and aldosterone secretion rates in lead-poisoned men than expected. The mechanism of action on the renin-aldosterone system was not known. Gonzalez et al. (1979) studied renin activity, aldosterone, and plasma potassium levels in a group of lead-intoxicated patients, who had low plasma renin activity (PRA) in response to a furosemide challenge (a volume-depleting stimulus) and were hyperkalemic (evidence that aldosterone levels were low). Bertel et al. (1978) also presented a clinical case report of reduced beta-adrenoceptor-mediated function in one lead-toxic man (blood lead >250 µg/dl) with hypertension (160-170/100-105 mm Hg). Prior to administration of the test dose of isoprenaline, the patient had high plasma norepinephrine levels and low PRA activity. The dose of isoprenaline required to increase heart rate 25 beats/min was 15-fold greater than that required in control subjects.

Recently, Campbell et al. (1985) found lead-related increases in the concentrations of PRA and angiotensin I in lead-exposed normotensive men. Mean plasma renin activity in these men was 8.3 ± 5.0 ng/ml/h, a value they note is slightly high for normotensive not on sodium restriction; all subjects with PRA >12 ng/ml/h had blood lead concentration of >2 µmol/l, the accepted upper limit for the general population. AI was positively correlated with PRA; it appeared that angiotensin converting enzyme was augmented with lead exposure, possibly by substrate induction due to increased AI concentration.

These authors point out that their findings appear to be in conflict with others which find depressed or unaltered renin activity in lead poisoning; however, the studies may not be comparable because the men in this study had chronic sub-clinical lead exposure as compared to chronic heavy lead exposure. None of the subjects in this study had excessive lead exposure--rather, exposure which would be considered "normal". Yet they tended to have elevated PRA, which may reflect possible low-grade stimulation of the renin-angiotensin-aldosterone system that, if continued through chronic cumulative exposure, might affect blood pressure in sensitive individuals.

There is another hormone system which has postulated effects in regulation of blood pressure: the kallikrein-kinin system (Carratero and Scicli, 1983). Kallikreins (found in plasma, urine and several glands, including the kidney) are proteases which release kinins from plasma substrates called kininogens. Kinins, thought to be antagonistic to AII, are vasoactive peptides which may participate in blood pressure regulation by altering vascular tone and regulating sodium and water loss. Kinins are inactivated by plasma kininases (one of which is angiotensin I converting enzyme). Urinary kallikreins can be measured by their esterolytic activity on synthetic substrates. Many reports suggest that urinary kallikrein is decreased in patients with essential hypertension, although others do not find such an association, and indeed find normal excretion rates.

Boscolo et al., (1981) studied urinary kallikrein activity and plasma renin activity in 22 men occupationally exposed to lead. Eight of these men who suffered from hypertension and/or nephropathy had low or absent PRA; this finding may be related to the presence of renal disease rather than be contributory to it. The remaining 14 non-symptomatic men showed normal or reduced urinary kallikrein and variable PRA. The authors concluded that the slight but significant correlation between renin and kallikrein that was found in the lead-exposed patients might be the result of a correlated physiological response of these renal enzymes due to an effect of lead on one or more components of the blood pressure regulating system.

The paucity of experimental data linking lead and changes in the renin-angiotensin system stimulated most of the following experimental studies, although many questions remain unanswered.

2.4 Experimental Studies of Lead Effects on Blood Pressure and the Renin-Angiotensin System

Several questions can be posed regarding how lead might affect the renin-angiotensin system, such as:

(1) Does lead affect sodium handling by the renal tubule?
(2) Does lead directly affect renin release? If so, is AII elevated to an appropriate level? Do normal homeostatic mechanisms function to adjust renin levels under conditions of fluid and electrolyte loss?
(3) Does lead alter renin synthesis (as measured by renal renin content)?
(4) Does lead affect rate of production of AII by altering angiotensin converting enzyme activity?
(5) Does lead alter AII catabolism?
(6) Does lead affect renin substrate production?
(7) Does lead affect renin clearance by the liver?
(8) Does lead affect vascular reactivity directly?
(9) Does lead directly affect aldosterone release?
(10) Does lead alter noradrenergic activity (either in adrenal glands or systemically)?

Many of these questions have been addressed by studies discussed below.

2.4.1 Acute In Vivo Lead Exposure

Lead injected iv in dogs and rats, at doses as low as 0.1 mg/kg (whole blood lead < 5 µg/dl and renal lead of 1.2 µg/g) produced over the next several hours significant increases in plasma renin activity (PRA) and in excretion of sodium, other cations, and water (Mouw et al., 1978). There was no change in glomerular filtration rate; therefore, the increased sodium excretion could be attributed to decreased sodium reabsorption. The mechanism of lead's action on tubular reabsorption was not determined, but it was suggested (though not evaluated) that lead could affect mitochondrial ATP production necessary for active transport processes or act directly on carrier molecules or enzymes, e.g., Na^+/K^+-ATPase, specifically involved in tubular transport. In this report, the mechanism by which lead increased renin secretion was not determined.

In a subsequent study, Goldman et al. (1981) found that the rise in PRA after acute lead injection was not due to increased renin secretion in six of nine dogs; rather, there was elimination of hepatic renin clearance, without evidence for other interference in liver function. In the remaining three dogs, renin secretion increased; this was thought to be due to lead activation of normal mechanisms for renin secretion, although none of the classic pathways for influencing renin secretion were altered. The authors postulated that lead might produce alterations in cytosolic calcium concentration in renin-secreting cells. (Further evidence that cytosolic calcium concentration is indeed important in renin release has been reviewed in detail by Churchill, 1985.) In addition, although angiotensin II (AII) levels in lead-exposed animals were elevated because of increased PRA, the AII levels were not increased proportionately as much as the PRA, leading to a further suggestion that angiotensin-converting enzyme (which converts AI to AII) might be suppressed or that AII-degrading enzyme could be enhanced; this was not tested in the experiment. The authors postulate that there may be multiple actions of lead on the renin-angiotensin system which may help explain confusion about the ability of lead to cause hypertension. At certain exposure conditions, there could be elevated PRA without simultaneous inhibition of angiotensin-converting enzyme, thereby contributing to hypertension, while higher doses or longer exposure might inhibit converting enzyme and thereby cause loss of hypertension. Neither hypothesis was addressed in this experiment.

2.4.2 Chronic Lead Exposure

The literature of experimental findings of lead-induced changes in the renin-angiotensin system and blood pressure in animals is complicated by apparently inconsistent results when comparing one study to another. All studies report changes in the renin-angiotensin system, yet some studies fail to find an effect on blood pressure and others do report hypertension. Doses and exposure periods employed vary widely, but in general, hypertension is observed most consistently with relatively low doses over relatively long exposure periods. The papers reviewed here make specific mention of lead dose employed and blood lead concentration achieved (if measured). For comparison with human exposure findings, it is helpful to recognize that blood lead concentrations seldom exceed 40 μg/dl in the general population.

Perry and Erlanger (1978) found that chronically feeding rats either cadmium or lead at doses of 0.1, 1.0, or 5.0 ppm produces statistically significant increases in systolic blood pressure. Blood lead concentrations were not determined in this experiment. There were dose-dependent changes in blood pressure, measured at 3 months, and the increase observed with 5 ppm Pb was observed at 3, 9, and 18 months of observation. Body burden of lead in rats fed 0.1 ppm Pb was estimated to be 0.4 mg at 18 months. The mechanisms for this finding were not discussed but the implications for human populations exposed to very low doses of these metals were pointed out. Victery et al. (1982a) reinvestigated the question, using lead doses of 100 and 500 ppm administered in the drinking water to rats beginning while animals were *in utero* and continuing through six months of age. At 3½ mo of age, the male rats drinking 100 ppm lead first demonstrated a statistically significant increase in systolic blood pressure (152 ± 3.7 vs. 135 ± 5.6 mm Hg); this difference persisted for the remainder of the experiment. Animals drinking 500 ppm had lower pressures which were not significantly different from controls. Female rats drinking 100 ppm did not demonstrate pressure changes. At termination of the experiment PRA was significantly decreased by 100 ppm lead exposure, but not at 500 ppm. AII values tended to be lower (controls: 22 ± 8 pg/ml, 100 ppm: 13 ± 7, 500 ppm: 10 ± 2). There was a dose-dependent decrease in AII/PRA ratio for lead-exposed rats. Renal renin was depressed in lead-exposed animals. The hypertension observed in these animals was not secondary to overt renal disease (as opposed to an effect on renal cell metabolism), as evidenced by lack of changes in renal histology and plasma creatinine.

With regard to possible mechanisms of the lead-induced hypertension, the animals had low-renin hypertension (which is characteristic of 30 percent of people with hypertension). Thus, elevated renin was not responsible for maintenance of the hypertension. Volume expansion may be a factor, as suggested by slight increases in body weight and decreased hematocrit (also possibly related to lead effects on heme synthesis). There was no change in plasma sodium and potassium, although more sensitive determinations of fluid balance and exchangeable sodium were not done. A second potential hypertensive mechanism, increased vascular responsiveness to catecholamines, was examined and is discussed below.

Victery et al. (1983) examined changes in the renin-angiotensin system of rats exposed to lead doses of 5, 25, 100, or 500 ppm during gestation until 1 month of age. All had elevated plasma renin activity, while those at 100 and 500 ppm also had increased renal renin concentration. Lead-exposed animals anesthetized to obtain the blood sample secreted less renin than control animals. It appears that lead has two chronic effects on renin secretion, one inhibitory and one stimulatory; the magnitude of effect on PRA reflects the dose and timing of the lead exposure as well as the physiological state of the animal.

In another study, Victery et al. (1982b) reported that rats fed 5 or 25 ppm lead for 5 months (blood lead of 5.6 and 18.2 μg/dl, respectively) did not develop hypertension but at 25 ppm had significantly decreased PRA. Both groups of animals had a decrease in the AII to PRA ratio. Thus, lead exposure at levels generally present in human population caused observable effects in renin synthesis, and produced changes in AII concentration which were consistent with either inhibition of conversion of AI to AII or enhanced AII catabolism. No measurements of ACE activity were made. The failure to observe hypertension in these animals may have been due to a number of factors, but additional studies may be required to verify this finding.

Iannaccone et al. (1981) administered 50 ppm lead to male rats for 160 days (average blood lead of 38.4 μg/dl) and found a marked increase in arterial pressure of lead-exposed animals (systolic/diastolic: 182±6/138±7 mmHg) versus pressures in controls of 128±5/98±3. No measurements of hormone levels were performed; determination of vascular reactivity in these animals is discussed below.

Male pigeons fed a diet containing added calcium (100 ppm), magnesium (30 ppm), lead (0.8 ppm), or cadmium (0.6 ppm) in a 2x4 factorial design for a six-month period were observed for alterations in aortic blood pressure and atherosclerotic changes (Revis et al., 1981). Diastolic pressures were 25 mm Hg higher in pigeons exposed to Mg, Pb, or Cd than in Ca-exposed pigeons. Systolic pressure was greatest in Cd-exposed birds. Calcium in the diet resulted in lowered systolic pressures in animals exposed to combinations of other metals (presumably by decreasing their gastrointestinal absorption). Similarly, there was a decrease in number and size of aortic plaques in presence of calcium and an increase with lead exposure.

Keiser et al. (1983b) tested lead-exposed rats (500 or 1000 ppm for 3-4 mo, blood lead levels of 41 and 55 μg/dl) for the ability of the liver to clear exogenous renin and a test substance (sulfobromophthalein) following nephrectomy. They found no difference from control clearance times. Thus, elevations in plasma renin observed in chronically exposed animals must be the result of increased renin secretion. However, the finding of decreased renin activity after some long-term exposure periods (see above) illustrates that lead must also act in an inhibitory way to decrease renin secretion, and the finding of decreased, increased, or unchanged renin activity depends on the balance of the stimulatory and inhibitory input to the juxtaglomerular cells.

In a preliminary experiment, there were no differences in urinary kallikrein excretion rates in lead-exposed and control rats (Victery and Vander, unpublished findings).

2.4.3 Renin Secretion by Kidney Slices In Vitro

The effects of renin-secretion stimuli on the ability of kidney slices to secrete renin *in vitro* either after chronic *in vivo* or *in vitro* exposure to lead have been studied by several investigators. Keiser et al. (1983a) reported that rabbit kidney cortex slices exposed to 10^{-5} or 10^{-6} M lead secreted significantly less renin than controls. Slices obtained from lead-exposed rabbits (500 or 1000 ppm for 7 wk, with blood lead levels of 66 and 109 µg/dl respectively) secreted significantly more renin *in vitro* than controls. They postulated that lead could compete with Ca^{2+} for influx into juxtaglomerular cells and thereby stimulate renin release. Responsiveness to a beta-adrenergic stimulus was less in the higher-dose slices. Since β-adrenergic stimuli are thought to act via reduction of intracellular $[Ca^{2+}]$ (by increased Ca efflux or intracellular sequestration), it was proposed that lead may interfere with these calcium fluxes and interfere with the response to β agonists.

Meredith et al. (1985) found somewhat contradictory results, with lead able to provoke renin secretion from rabbit kidneys both *in vivo* and *in vitro* (at comparable dose levels to that used by Keiser). Calcium channel blockers attenuated this response. These authors propose that lead is able to act at the cellular level to stimulate renin secretion. Since most experimental evidence suggests that increased intracellular calcium decreases renin release, whereas calcium efflux stimulates renin secretion, the authors further postulate that lead uptake by the juxtaglomerular cells promotes calcium efflux which then leads to an increase in renin secretion.

2.4.4 Effects of Lead on Vascular Reactivity

Piccinini et al. (1977) and Favalli et al. (1977) studied the effects of lead on calcium exchanges in the isolated rat tail artery; lead in concentrations of up to 15 µmol *in vitro* produced contractions which required the presence of calcium in the perfusion solution. Therefore, calcium influx was not affected by lead. The fact that tissue calcium content was increased is compatible with the sites of lead action at the cell membrane; lead inhibits calcium extrusion, and at intracellular stores, lead decreases calcium-binding capacity. Both processes produce an increase in intracellular exchangeable calcium.

Tail arteries obtained from the hypertensive rats in the study performed by Victery et al. showed an increased maximal contractile force when tested *in vitro* with the alpha-adrenergic agents norepinephrine and methoxamine (Webb et al., 1981). This finding is apparently related to an increase in the intracellular pool of activator calcium in the smooth muscle cells in the artery. This change may also be responsible for decreased relaxation of the muscle after induced contractions.

In vivo tests of cardiovascular reactivity in rats exposed to 50 ppm lead (blood lead 38.4 ± 3.6 µg/dl) for 160 days were performed by Iannaccone et al. (1981). Systolic and diastolic blood pressure readings obtained under anesthesia were 182 ± 6/138 ± 7 mm Hg for lead-exposed rats versus 128 ± 5/98 ± 3 for controls. Humoral agents, i.e., norepinephrine and angiotensin II (but not bradykinin and angiotensin I), produced significant increases in systolic and diastolic pressure. This suggests there is decreased conversion of AI to AII. At high doses, epinephrine produced an equal increase in pressure in lead-exposed and control animals; at lower doses, only slight increases in mean arterial pressure were observed. Bilateral carotid artery occlusion under conditions of autonomic blockade produced a two-fold greater decrease in blood pressure and heart rate in lead-exposed rats. The data suggest that the lead-related increase in arterial pressure is due at least in part to greater sympathetic tone, with the metal affecting neural control of blood pressure.

2.4.5 Effects of Lead on Noradrenergic Hormones

Lead exposure alters the levels of noradrenergic hormones in the young animal exposed via maternal milk from birth until day 21 of age (Goldman et al., 1980). Lead concentrations in the drinking water of up to 2000 ppm produced blood lead levels in pups of 47 ± 3 µg/dl with dose-dependent increases in adrenal and plasma norepinephrine. There were also changes in several enzymes which alter turnover rates of norepinephrine. Baksi and Hughes (1983) investigated the effect of 6-wk tetraethyl lead exposure (at 0.2, 2.0, and 5 µg Pb/g food) on adrenal catecholamine levels and found significant decreases in dopamine (perhaps due to a decrease in synthesis) and significant increases in norepinephrine and epinephrine. Both of these groups of authors felt that the change in adrenal catecholamines could directly or indirectly be responsible for the hypertension observed in lead-exposed animals.

2.4.6 Effects of Lead on Cardiac Muscle

Lead has been hypothesized to contribute to cardiomyopathy (Asokan, 1974) and to have cardiotoxic properties. Rats fed 1 percent lead acetate for 6 weeks (with blood lead levels of 112 ± 5 µg/dl) had structural changes in the myocardium. These included myofibrillar fragmentation and separation with edema fluid, dilation of the sarcoplasmic reticulum, and mitochondrial swelling. These changes were observed before any measured changes in myocardial electrolyte concentrations.

Williams et al. (1977a,b) exposed young rats to 2000 ppm lead via maternal milk, from birth to 21 days of age (blood lead at 21 days of age was 43 µg/dl but was not different from controls at 170-200 days). Animals were studied for cardiovascular response to norepinephrine at 170-200 days of age. There were no differences in the blood pressure increase in response to norepinephrine, but there was a five- to ten-fold increase in cardiac arrhythmias in lead-exposed animals. There were no differences in the basal or norepinephrine-stimulated cyclic AMP levels in cardiac tissue.

In a subsequent study (Hejtmancik and Williams, 1979), it was reported that only part of the arrhythmogenic activity of norepinephrine in lead-exposed rats was due to reflex vagal stimulation; there was also a direct cardiac effect, probably at the alpha receptor level. Lead appeared to have no effect on beta receptors.

Kopp et al. (1978) developed an *in vitro* system for monitoring the cardiac electrical conduction system (electrocardiogram or ECG) and systolic tension, and demonstrated that *in vitro* lead (3×10^{-2} mM) or cadmium (3×10^{-2} mM) depressed systolic tension and prolonged the P-R interval of the ECG. Both ions increased conduction times in the His bundle electrograms but conduction blocks occurred at different sites (atrioventricular node for cadmium and distal to the His-Purkinje cell junction for lead).

In a subsequent paper, Kopp and Barany (1980) found that cadmium or lead added to heart tissue perfused *in vitro* (3×10^{-3} mM and 3×10^{-4} mM, respectively) inhibited the positive inotropic activation of the heart by calcium and isoproterenol, and the concomitant increase in phosphorylation of cardioregulatory proteins. There was no effect of lead or cadmium on the positive chronotropic effects of the beta-adrenergic agonist.

Hearts obtained from rats exposed to low levels of cadmium and/or lead (5 ppm) for 20 months were found to have similar changes in the heart's electrical conduction system (Kopp et al., 1980) with significant prolongation of the P-R interval. In lead-fed animals, this was due to increased conduction time through the His-Purkinje cell system.

Williams et al. (1983) suggested that much of the negative inotropic effect of lead on cardiac tissue and ECG abnormalities can be related to lead's interference with calcium ion availability and/or membrane translocation. In addition, even those lead exposure-related effects that appear to occur through autonomic nerves may be understood in terms of effects on calcium ion, which is required for neurotransmitter release.

Evis et al. (1985) studied the effects of chronic low lead treatment (5 and 25 ppm, with blood lead levels < 10 µg/dl) and hypertension (spontaneously hypertensive rats) on blood pressure and the severity of cardiac arrhythmias in rats. The animals were studied up to 16 months of age and the authors reported that there were no consistent lead-related effects on ischemia-induced cardiac arrhythmias, blood pressure, or P-R interval in the electrocardiogram.

Prentice and Kopp (1985) examined functional and metabolic responses of the perfused rat heart produced by lead with varying calcium concentrations in the perfusate. Lead altered spontaneous contractile activity, spontaneous electrical properties and metabolism of the heart tissue. The exact mechanisms were not completely resolved but did involve disturbances in cellular calcium metabolism, although not by any single mechanistic model. Other possible actions of lead were discussed, and they included: (1) lead-induced disturbances in calcium-dependent enzymatic processes; (2) altered calcium binding and calcium activation of phosphorylation-dependent events linked to transduction of chemical energy to produce mechanical work; (3) modified calcium release and sequestration by intracellular storage sites; and (4) disruptions in cellular energy production and utilization.

In addition, hearts perfused with 30 µM lead had reduced coronary blood flow, presumably by lead acting to directly constrict the vascular smooth muscle or by interference with the local metabolic stimuli for vasodilatation. Increases in perfusate calcium concentration partially reversed this effect, although at the highest calcium levels (5.0 mM), coronary blood flow was again reduced. These authors concluded that their present findings were consistent with those of others which showed increased vascular reactivity and that the chronic lead exposure-related changes in blood pressure may be related to localized actions of lead on vascular beds and arterial smooth muscle.

2.5 Summary of Lead-Related Effects on the Cardiovascular System

Blood pressure is regulated and affected by many interactive forces and control systems; some of these have been shown to be affected by lead exposure. Understanding of the effects of lead on each system is still preliminary, but sufficient evidence indicates that changes which occur in the presence of lead can promote development of hypertension. To briefly summarize, lead can directly inhibit renal tubule reabsorption of sodium, probably via action on the Na^+/K^+-ATPase. Sodium/potassium-ATPase inhibition may occur in other cell types as well. This may alter the concentrations of intracellular sodium and calcium ions. Some volume depletion may occur which may act to elevate plasma renin activity. The effect of lead exposure on plasma renin activity can be stimulatory, inhibitory, or without effect, depending on the length of exposure and the exposure level. Lead exposure reduces the increase in PRA that occurs with noradrenergic stimulation. Hepatic clearance of renin is not affected by lead exposure and is thus apparently not responsible for an increase in PRA during chronic lead exposure. Depending on the length and dose of lead exposure, renal renin concentration is elevated followed by decreased concentrations. Changes in renin secretion rate in animals do not appear to be well correlated with changes in blood pressure and may, in fact, reflect altered homeostatic responses elicited to regulate pressure.

Additional changes observed during lead exposure include the following: in response to elevations in PRA, AII is elevated, but the levels are inappropriately low; this does not appear to be due to a lead-related decrease in ACE (angiostensin-converting enzyme), but rather to increased catabolism. Aldosterone levels are also inappropriately low, possibly due to a lead-related defect in calcium ion-dependent release of aldosterone. Adrenergic hormones are elevated. Vascular smooth muscle isolated from lead-exposed animals has increased reactivity to noradrenergic stimuli, probably due to an increase in intracellular calcium ion concentration. There appears to be increased sympathetic activity in lead-exposed animals. Cardiac arrhythmias are usually observed to be more frequent in lead-exposed animals.

Although the exact mechanisms involved in lead-induced changes in renin secretion rate have not been examined, it is likely that lead could be affecting the cytosolic free calcium ion of the juxtaglomerular cells. When there is a stimulation of renin release, there is presumably a decrease in intracellular [$Ca^{2}+$] due to lead blockage of calcium entry through voltage-sensitive calcium channels. After lead enters the juxtaglomerular cells, lead could enhance or block calcium exit via Na/Ca exchange pumps, or increase or decrease the intracellular sequestration of calcium in storage compartments. It is not yet clear whether lead stimulates or antagonizes calcium fluxes that occur in the JG cells; therefore it is not possible to state definitely which of these possibilities is correct. Renin release in response to adrenergic stimuli binding to receptor-operated calcium channels appears to be inhibited. The reasons for this are not known, but lead may decrease the number of receptor sites or change the intracellular calcium response which is normally elicited when these channels are stimulated. For example, if intracellular free calcium ion levels are already elevated and there were to be a smaller decrease in [$Ca^{2}+$] than normal due to blocking of calcium efflux via the Na/Ca exchange pumps or lowered pumping into intracellular stores, renin secretion would be less under conditions of adrenergic stimulation.

The changes in vascular reactivity which have been reported in animals chronically exposed to lead are probably the key finding which can lead to an understanding of how lead can contribute to development of hypertension. The vascular smooth muscle changes are necessary and sufficient in themselves to account for the increase in blood pressure and the fact that these changes are observed in animals exposed to relatively low lead levels makes it increasingly important to evaluate these findings in additional experimental studies. There may be additional changes in the entire sympathetic neural control of vascular tone which acts to amplify the contractile response to any endogenous vasoconstrictor substance.

Two authors (Audesirk, 1985, and Pounds, 1984) have recently reviewed experimental evidence on the influence of lead on calcium movements at the subcellular level in a variety of cell types (including neurons, neuromuscular synapses, and hepatocytes). The reader should consult these reviews for experimental documentation of the postulated changes in calcium-activated systems. Lead may interact with any process normally influenced by calcium ions and, depending on the system, lead may act as a calcium antagonist or as an agonist. In addition, lead interferes with the function of many proteins, especially enzymes such as Na/K ATPase and the mitochondrial respiratory enzymes. These interactions may influence calcium ion concentrations and movements. If lead interferes with calcium ion movement through calcium channels, either by blocking entry or blocking efflux, there will be a decrease or an increase in cytosolic free calcium ion. Lead may alter the distribution and uptake rates of calcium ion in cell storage sites with the result that mitochondrial and endoplasmic reticulum levels can be increased or decreased; this in turn would affect cytosolic free calcium levels. Lead binds to calcium-binding sites on calcium regulatory proteins (calmodulin, in particular [Cheung, 1984]) and thereby can alter enzyme systems such as Ca-specific ATPase, which would then alter calcium efflux from the cytosol.

This review has discussed some of the major experimental data concerning lead-related changes in blood-pressure regulatory systems. Further research efforts are necessary to evaluate more fully cellular mechanisms by which lead exposure produces its effects. Lead (even at very low levels) produces measurable effects on the renin-angiotensin system. With the blood pressure changes observed in lead-exposed animals, changes in renin are not established to be the cause of hypertension; rather, hypertension is more likely to be due to changes in vascular reactivity and level of sympathetic tone, both of which may be dependent on lead-related changes in intracellular calcium ion concentration.

3. EFFECTS OF LEAD ON DEVELOPMENT AND GROWTH

The effects of lead exposure early in development have recently become a matter of increasing interest and potential concern in light of certain newly published epidemiologic observations. Coupled with earlier findings from human and experimental animal studies, these recent results point toward a number of deleterious effects on various aspects of development and growth associated with relatively low exposure levels encountered by the general population. For convenience, the findings are grouped here under the headings of fetal exposure effects and postnatal growth effects.

3.1 Fetal Exposure Effects

Numerous investigations evaluating the effects of intrauterine lead exposure on fetal development are reviewed in Section 12.6 of the revised Criteria Document (U.S EPA, 1986). Animal studies reviewed there tended to use rather high exposure levels and were sometimes confounded by nutritional variables, but such studies collectively provide clear evidence that prenatal lead exposure can cause a number of fetotoxic and teratogenic effects. Among the specific effects observed are reduced heme synthesis and decreased fetus size or weight. Changes in heme metabolism--reduced ALA-D activity, in particular--have also been reported for humans perinatally, even at average blood lead levels of only 8 and 10 µg/dl in the infants and their mothers, respectively (Lauwerys et al., 1978). Some additional human studies have provided evidence suggestive of an association between prenatal lead exposure and shortened gestation, decreased birth weight, or stillbirths (e.g., Fahim et al., 1976; Nordstrom et al., 1979; Khera et al., 1980b), but others have found no significant association between such effects and prenatal lead exposure (e.g., Clark, 1977; Alexander and Delves, 1981; Roels et al., 1978).

Part of the difficulty in drawing conclusions from many of the human studies, especially the earlier ones, derived from the problems in accurately measuring blood lead levels (see Chapter 9 of the revised 1986 Criteria Document) and in identifying and controlling confounding variables. In addition, the power of these early studies was often limited by the small number of subjects employed. More recently, several new human studies, using improved analytic techniques and, in general, rather large numbers of subjects, have focused on possible associations of prenatal lead exposure and various developmental outcomes in fetuses, infants, or young children. These studies, most of them longitudinal in design, have generally estimated prenatal lead exposure through maternal or cord blood lead concentrations and have followed (or are still following) the children's postnatal exposure through periodic blood lead measurements. The studies have also been careful to consider various confounding factors that could affect developmental endpoints.

3.1.1 Results of Recent Human Studies

Using logistic regression modeling techniques, Needleman et al. (1984) found an association between umbilical cord blood lead levels and certain minor congenital anomalies based on hospital records for 4354 infants born in Boston. Their analysis controlled for a number of demographic, socioeconomic, and other possible confounders, including coffee, alcohol, tobacco, and marijuana use, and variables such as gestational age, birth weight, maternal parity, and age. The most common anomalies included hemangiomas and lymphangiomas (14/1000 births), hydrocele (27.6/1000 males), minor skin anomalies such as skin tags and papillae (12.2/1000 births), and undescended testicles (11/1000 males). A statistically significant association was found between cord blood lead levels and the occurrence of minor malformations taken collectively. However, no individual type of malformation showed a significant relationship to lead exposure, nor were major malformations found to be significantly related to lead. Birth weight and gestational age also showed no evidence of being related to lead exposure.

On the other hand, first trimester bleeding, premature labor, and neonatal respiratory distress were all significantly reduced at higher exposure levels of lead.

Moore et al. (1982) reported that gestational age was significantly reduced as a function of increasing cord or maternal blood lead levels in a cross-sectional study of 236 mothers and their infants in Glasgow, Scotland. Blood lead levels were relatively high in the 11 cases of premature birth (gestational age less than 38 weeks) that were observed in this study: maternal levels averaged about 21 μg/dl and cord levels about 17 μg/dl (geometric means). Overall, the geometric mean blood lead level for the mothers was approximately 14 μg/dl and for the infants was approximately 12 μg/dl. Stepwise forward multiple regression analyses using log-transformed blood lead levels revealed significant negative coefficients for length of gestation against maternal blood lead (-0.056, $p < 0.01$) as well as cord blood lead (-0.047, $p < 0.05$). Other variables considered in the analyses included: mother's age, social class, birth weight, and total parity, of which only total parity was also significant. First-flush household water lead levels were positively associated with both maternal and cord blood lead levels ($p < 0.001$).

A recent paper by Bryce-Smith (1986) noted that both birth weight and head circumference were reduced as a function of placental lead levels in a cohort of 100 normal infants born in Yorkshire, England. Placental lead concentrations averaged between 1 and a little more than 2 μg/g. Zinc and cadmium levels also showed significant relationships to birth weight and head circumference. Little information is provided on the details of the work, but a full account of the study is said to be in preparation for publication.

A longitudinal study of the effects of lead exposure on child development is underway in the lead smelter town and environs of Port Pirie, South Australia. McMichael et al. (1986) enrolled 831 pregnant women and followed 774 of the pregnancies to completion (spontaneous abortion, stillbirth, or live birth). Venous blood lead concentrations were measured in the mothers at least three times during pregnancy: at 14-20 weeks, around 32 weeks, and at delivery. In addition, cord blood lead was measured. Blood lead levels were significantly higher in the Port Pirie women than in those from adjacent towns and countryside (e.g., 11.2 μg/dl at delivery in Port Pirie versus 7.5 μg/dl outside). Mean blood lead values did not vary systematically through the course of pregnancy. Information on demographic and socioeconomic characteristics, medical and reproductive history, smoking and drinking habits, and other variables was collected by a standardized questionnaire-interview. A number of pregnancy outcomes were assessed. Most notably, multivariate analysis showed that pre-term delivery was significantly related to maternal blood lead at delivery. Pre-term delivery was defined as birth before the 37th week of pregnancy, and was measured by date of last menstrual period as well as by the Dubowitz et al. (1970) assessment of neonatal maturity. As shown in Table A-4, the relative risk of pre-term delivery increased over four-fold at

Table A-4. Estimates of relative risk of pre-term delivery (by last menstrual date) based on multiple logistic analysis of maternal blood lead concentrations at delivery.

Maternal PbB (μg/dl)	Relative risk	
	Including stillbirths	Excluding stillbirths
≦8	1.0	1.0
>8, ≦11	2.1	2.7
>11, ≦14	3.0	6.1
>14	4.4*	8.7

*Significantly different from 1.0 based on 95% confidence interval of 1.2-16.8; confidence intervals not reported for relative risks excluding stillbirths.

Source: McMichael et al. (1986)

blood lead levels above 14 μg/dl. If cases of late fetal death are excluded, the association is even stronger and the relative risk due to lead exposure even greater (see Table A-4).

McMichael et al. assessed a number of other outcomes as well. Of 774 pregnancies, 23 ended in spontaneous abortion before the 20th week. All but one of these miscarriages occurred in the higher-exposure Port Pirie group. Thus, although the Port Pirie mothers constituted less than 80 percent of the study population, they accounted for about 96 percent of the spontaneous abortions. McMichael et al., however, limited their statistical analysis to the Port Pirie group alone and found no significant association between spontaneous abortions and maternal blood lead levels, mother's age, blood pressure, or certain other variables. Of 740 non-twin pregnancies greater than 20 weeks, 11 ended in stillbirth. Ten of the 11 occurred in Port Pirie women. The proportion of stillbirths was 17.5/1000 live births in Port Pirie versus 5.8/1000 outside Port Pirie and 8.0/1000 for South Australia overall. Interestingly, maternal blood lead levels at 14-20 weeks did not differ appreciably for stillbirth versus live birth pregnancies, but at delivery the maternal blood lead level for stillbirths was significantly lower (7.9 μg/dl) than that for live births (10.4 μg/dl).

As for neonatal morphology, the incidence of low birth weight (i.e., <2500 g at gestational age 37 weeks or more) was greater in the Port Pirie group (3.9 percent) than in the non-Port Pirie group (1.8 percent). However, both maternal blood lead at delivery and cord blood lead were consistently lower (although not significantly so) in low birthweight pregnancies. Head circumference was significantly inversely related to maternal blood lead (-0.03 cm per μg Pb/dl), but the authors suggested that this finding could have been an artifact of procedural differences between hospitals. Crown-heel length was not associated with lead exposure. After controlling for certain risk factors, such as smoking and alcohol usage, no association between lead exposure and the occurrence of congenital anomalies was evident. Difficulty in conceiving and premature rupture of membranes showed no association with lead exposure; but for 15 deliveries with incomplete placental membranes, the mean maternal blood lead level at delivery was 13.4 µg/dl, versus 10.7 µg/dl for all other pregnancies.

Other recent prospective studies have also assessed physical development but have placed particular emphasis on neurobehavioral aspects of child development. The Bayley Scales of Infant Development have been frequently used to assess mental and psychomotor development in these studies because they are well suited for children 2 to 30 months of age and have satisfactory reliability and validity.

Bellinger et al. (1984) were the first to report effects on Bayley Mental Development Index (MDI) scores that were inversely related to cord blood lead levels. The subjects were 216 middle- to upper-middle-class Boston children, 90 percent of whom had cord blood lead levels below 16 µg/dl (the highest being 25 µg/dl). Subjects were grouped into three categories: low (mean = 1.8 µg/dl); mid (mean = 6.5 µg/dl); and high (mean = 14.6 µg/dl). Multivariate regression analyses were used to model effects on the MDI. Of the several covariates examined, HOME scores (Bradley and Caldwell, 1979) and length of gestation were identified as confounders of the association between cord blood lead and the MDI; both were positively correlated with cord blood lead and with the MDI, but not significantly so. The effect of this positive relationship was to reduce the degree of association between cord blood lead levels and MDI scores. Thus, when length of gestation and HOME scores were partialled out, the bivariate correlation between cord blood lead and the MDI increased from -0.11 to -0.19. In terms of covariate-adjusted MDI scores, the difference between low and high lead groups was nearly 6 points (see Table A-5).

As the longitudinal study by Bellinger et al. (1985; 1986a,b) has continued, the association between higher cord blood lead and lower Bayley MDI scores has persisted to 24 months, at which point the deficit in MDI performance was still approximately 5 points (Table A-5). No association was found using postnatal blood lead levels, nor did the Bayley Psychomotor Development Index show an effect.

Some of the first results of a longitudinal study of inner-city children born in Cincinnati, Ohio, have been reported by Dietrich et al. (1986). These are interim results for 185 subjects from a cohort of approximately 400 subjects. The investigators measured blood lead concentrations of the mothers at the first prenatal visit (PbB-Pre), generally in either the first or second trimester of pregnancy, and of the infants at 10 days, 3 months, and 6 months after birth (PbB-1, -3, and -6). The mean PbB-Pre was 8.3 µg/dl (range: 1-27 µg/dl); infant PbB-1, -3, and -6 mean averages were 4.9, 6.3, and 8.1, respectively (overall range: 1-36 µg/dl). The Mental Development Index, Psychomotor Development Index (PDI), and Infant Behavior Record (IBR) of the Bayley Scales were administered at 6 months. Multivariate analyses indicated an inverse association between blood lead levels at 3 months and

Table A-5. Covariate-adjusted Bayley Mental Development Index scores of infants classified by umbilical cord blood lead levels.

Cord PbB (μg/dl)	Age (months)			
	6	12	18	24
<3	110.8 ± 1.2*	114.6 ± 1.5	114.3 ± 1.8	117.2 ± 1.7
6-7	107.1 ± 1.3	114.0 ± 1.6	115.4 ± 1.9	118.8 ± 1.8
≧10	105.0 ± 1.4	107.3 ± 1.6	110.3 ± 2.0	111.8 ± 1.8
Parameter estimate† ± standard error	-2.9 ± 0.9	-3.6 ± 1.1	-2.0 ± 1.4	-2.7 ± 1.3
p-value	0.0019	0.0015	0.15	0.038
95% confidence interval	-1.1 to -4.7	-1.4 to -5.8	0.7 to -4.6	-0.2 to -5.2

*Mean ± standard error

†Parameter estimate represents the estimated difference in mean covariate-adjusted MDI scores of adjacent exposure categories. The lowest and highest exposure categories may be compared by multiplying the parameter estimate by two.

Source: Bellinger et al. (1985)

performance on the MDI, PDI, and Attention/Motor Maturity factor of the IBR. However, these effects were evident only for the White infants, who constituted about 15 percent of the study population. Otherwise, no effect was evident for prenatal or postnatal exposure, either in White or Black infants.

Further analyses using a method known as structural equation modeling (based on regression techniques) indicated that prenatal lead exposure had an indirect effect on MDI and PDI scores through its effects on gestational age and/or birth weight (measured as continuous variables). That is, higher PbB-Pre levels were associated with reduced gestational age and reduced birth weight ($p < 0.05$ in each case), which in turn were both significantly associated with reduced MDI and PDI scores (see Figure A-2). Thus, although the net effect of prenatal lead exposure was evident in neurobehavioral deficits, the outcome was mediated through decreases in gestational age and/or birth weight. (Gestational age and birth weight were independently affected by lead exposure, even though gestational age may have determined birth weight to some extent). PbB-1 showed a similar relationship to MDI scores, but the regression coefficients were not as large as for PbB-Pre. Structural equation analyses also indicated that tobacco and alcohol usage may reduce birth weight both directly and (through association with prenatal blood lead) indirectly. However, the effect of prenatal blood lead

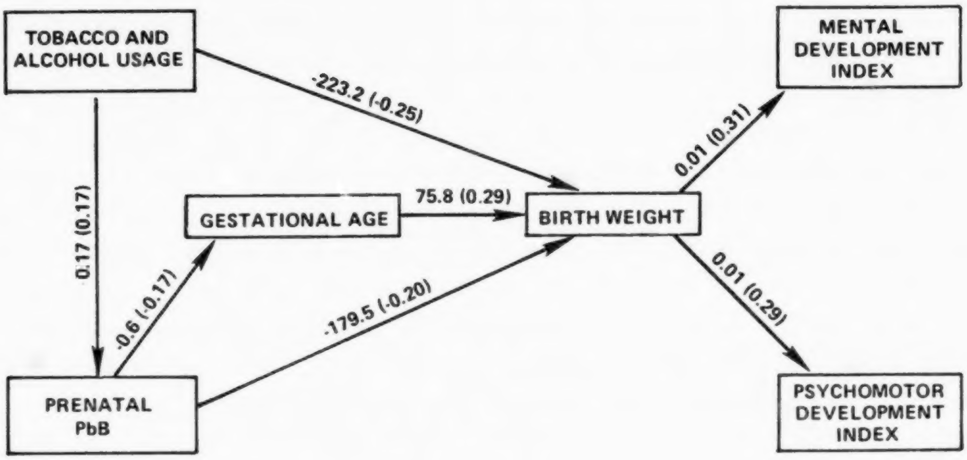

Figure A-2. Relationships among variables affecting 6-month MDI and PDI scores, as revealed through structural equation analyses. Arrows represent hypothesized relational pathways, with covariate-adjusted parameter estimates (and standardized regression coefficients) indicated for each. All relationships are significant at $p<0.05$ (one-tail test).

Source: Dietrich et al. (1986).

on gestational age and birth weight, and hence MDI and PDI scores, remained statistically significant even after adjustment for alcohol and tobacco usage. Race was not a significant confounder or covariate for prenatal lead exposure according to the authors' multivariate regression analyses and therefore was not evaluated in the structural equation models.

It should be noted that Dietrich et al. (1986) also found that higher 6-month blood lead levels were significantly associated with higher Bayley scores, particularly the PDI. They interpreted this association as the result of motorically advanced infants' (indicated by higher PDI scores) coming into greater contact with lead in their immediate surroundings. Post hoc analyses supported this view, for those infants with the greatest increase in blood lead levels between 3 and 6 months tended to have higher PDI scores at 6 months ($r = +0.21$, $p < 0.01$). As summarized by the authors, "while low level fetal exposure to lead may both directly (in the case of white subjects) and indirectly (for all infants) compromise neurobehavioral status at 6 months, more precocious infants may actually display higher blood lead levels when postnatally exposed to sources of lead in their physical environment." It remains to be seen what the ultimate developmental outcome is for such children.

In a continuation of the Port Pirie study described above, Vimpani et al. (1985) have reported preliminary results of testing 592 children at age 24 months on the MDI and PDI Bayley Scales. In addition to prenatal maternal and cord blood lead levels, capillary blood lead levels at 6, 15, and 24 months were assessed. Geometric mean blood lead levels rose sharply from about 14 µg/dl at 6 months to around 21 µg/dl at 15 months. About 20 percent of the subjects had estimated blood lead concentrations above 30 µg/dl at 24 months, after which levels declined slightly. Among the sociodemographic variables assessed were mother's age, each parent's education level and workplace, marital status, and the child's birth rank. HOME and maternal IQ were assessed when the children reached 3 years of age.

Pearson correlation coefficients between MDI scores and blood lead measures were statistically significant at all sampling stages except for delivery and cord blood. Multiple regression analyses using a number of sociodemographic and other potential covariates (e.g., 5-minute Apgar score, size for gestational age, mouthing behavior, maternal IQ) entered prior to blood lead indicated that reduced MDI scores were significantly associated with higher integrated postnatal blood lead levels but not with prenatal or perinatal levels. As shown in Table A-6, regression coefficients for specific postnatal sampling points (6, 15, and 24 months) were mixed in their significance levels, the highest occurring at 6 months and the lowest at 24 months (after controlling for maternal IQ). At the time of this preliminary report, maternal IQ had not been measured for the entire cohort; HOME scores were not included in any of the reported analyses.

A recent study by Ernhart et al. (1985a, 1986) has also addressed the issue of prenatal lead exposure and postnatal neurobehavioral function. Maternal and cord blood samples were obtained at the time of delivery in a Cleveland, Ohio, hospital. The mean blood lead level for 162 umbilical cord samples was 5.8 µg/dl (range: 2.6-14.7 µg/dl); mean blood lead level for 185 maternal samples was 6.5 µg/dl (range: 2.7-11.8 µg/dl). Of these totals, there were 132 mother-infant pairs of data, for which the correlation of blood lead levels was 0.80. In addition to size, minor morphological anomalies, and 1- and 5-minute Apgar performance, the infants were evaluated on the Brazelton Neonatal Behavioral Assessment Scale (NBAS) and part of the Graham-Rosenblith Behavioral Examination for Newborns (G-R). The NBAS Abnormal

Table A-6. Partial linear regression coefficients for 24-month Bayley MDI scores against each blood lead measure, with and without maternal IQ in the model†

PbB Index	Ignoring maternal IQ	Controlling For maternal IQ
Average Prenatal	-0.250	-0.064
Delivery	0.181	0.001
Cord	0.053	0.026
6 months	-0.231*	-0.396*
15 months	-0.084	-0.103
24 months	-0.152*	-0.061
Integrated Postnatal	-0.240*	-0.310*

†Model contains 13 sociodemographic and neonate factors

*Statistically significantly different from zero at $p \leq 0.05$ (one-tailed)

Source: Vimpani et al. (1985)

Reflexes scale focused on neonatal neuromuscular indicators such as walking, standing, Babinski reflexes, and ankle clonus. The G-R scales included a Neurological Soft Signs scale (jitteriness, high-pitched/weak cry, hypersensitivity, etc.) and a Muscle Tonus scale. Several covariates were incorporated in the hierarchical regression analysis, including alcohol, tobacco and drug use, nutrition, gestational age, and parental size measures.

Of the 17 neonatal outcomes examined, three measures showed significant relationships to blood lead measures. Abnormal Reflexes and Neurological Soft Signs showed significant increases in the amount of variance that cord blood lead accounted for; Muscle Tonus scores showed significant effects only for maternal blood lead levels (see Table A-7). Further analyses using data solely from mother-infant pairs showed only Neurological Soft Signs to be significantly related to cord blood lead; maternal blood lead showed no significant relationship (Table A-7). This dissociation of maternal and cord blood lead effects, despite the rather high correlation of the two independent variables, was viewed by Ernhart et al. as evidence of possible increased fetal accumulation of lead. With regard to morphological anomalies, Ernhart et al. found no evidence of any effects related to lead. However, they did find clear evidence of such effects related to maternal alcohol consumption (Ernhart et al., 1985b).

A brief report on later outcomes in this same cohort mentions a statistically significant effect of the Neurological Soft Signs measure on Bayley MDI scores at 12 months (Wolf et al., 1985). Apart from this indirect effect of cord blood lead, no effects on MDI scores at 6-24 months or Stanford-Binet IQ scores at 36 months were attributed to prenatal lead exposure. A more detailed account of the later stages of this prospective study will be needed to evaluate its findings and their implications.

Table A-7. Lead-related variance increments for neonatal neurological measures.

Variable	Cord PbB			Maternal PbB		
	Covariate Variance	Pb Effect Variance	p†	Covariate Variance	Pb Effect Variance	p†
All Available Data*						
Abnorm. Refl.	0.07	0.033	0.023	0.07	0.002	0.563
Neur. Soft Sign	0.05	0.038	0.016	0.04	0.004	0.408
Muscle Tonus	0.13	0.008	0.260	0.09	0.024	0.035
Restricted Data (132 paired cases)						
Abnorm. Refl.	0.09	0.006	0.373	0.09	0.001	0.717
Neur. Soft Sign	0.06	0.056	0.008	0.06	0.007	0.354
Muscle Tonus	0.12	0.015	0.162	0.12	0.016	0.153

†p values <0.05 are underlined.

*For cord PbB, n = 162; for maternal PbB, n = 185.

Source: Ernhart et al. (1985a)

The predictive value of different markers of lead exposure for neurobehavioral performance has been specifically addressed by Winneke et al. (1985a,b). Of an original study population of 383 children born in Nordenham, F.R.G., 114 subjects were followed up at age 6-7 years. The mean average maternal blood lead level was 9.3 µg/dl (range: 4-31 µg/dl); the mean cord blood lead level was 8.2 µg/dl (range: 4-30 µg/dl). Because of the high degree of correlation between cord blood and maternal blood lead (r = 0.79), the two were combined to form an estimate of perinatal exposure. Cord blood versus blood lead levels at age 6-7 yr correlated at r = 0.27. Stepwise multiple regression analyses by Winneke et al. (1985a) indicated that maternal blood lead levels accounted for nearly as much of the variance in neurobehavioral test scores at age 6-7 years as did contemporary blood lead levels (see Table A-8). Cord blood lead alone, however, showed less impact on later performance. Combining maternal and cord blood lead levels to form an estimate of perinatal exposure resulted in a significant association with only version 10 of the Wiener (Vienna) reaction performance test (Winneke et al., 1985b).

3.1.2 Interpretation of Findings from Human Studies

As reviewed above, three recent studies have investigated an association between prenatal lead exposure and congenital morphological anomalies (Table A-9). All three studies

Table A-8. Percent additional variance accounted for by different indices of lead exposure for selected neurobehavioral tests, as determined by stepwise multiple regression analyses after correction for confounding.

	Marker of Lead Exposure		
Test	Perinatal PbB	Cord PbB	Current PbB
WISC			
Verbal IQ	+0.2†	-0.1	+0.3
Performance IQ	+0.0	+1.8	-2.4*
Full-scale IQ	-0.1	+0.3	-0.3
Wiener Reaction Performance			
Version 12 errors	+2.8**	+0.7	+4.3***
Version 10 errors	+7.5***	+3.0**	+11.0***
Cued Reaction Time (3-sec)			
Lift-off latency	-2.5*	-1.4	+0.0
Push button latency	+3.8**	-0.7	-0.1

†Sign (+ or -) indicates direction of effect.

*p <0.10 **p <0.05 ***p <0.01

Source: Winneke et al. (1985a)

Table A-9. Summary of recent studies on the relationship between prenatal lead exposure and congenital malformations.

Reference	n	Pb-Exposure Index	Avg. PbB (μg/dl)	Malformations
Ernhart et al. (1985a, 1986)	185	delivery	6.5	0
	162	cord	5.8	0
Needleman et al. (1984)	4354	cord	6.5	+*
McMichael et al. (1986)	749	prenatal	11.0	0
		delivery	11.0	0
		cord	10.0	0

Symbols: 0, no evident relationship; +, positive relationship; -, negative relationship; *, statistically significant at p <0.05.

used regression analyses to control for numerous possible covariates and confounders, including mother's age, parity, and tobacco and alcohol usage. Nutritional information was collected by McMichael et al. (1986) and by Ernhart et al. (1985a, 1986), but apparently not by Needleman et al. (1984).

Of the three studies, only Needleman et al. (1984) reported significant effects related to lead exposure. The sole deleterious effect was for minor malformations as a group, not individually. Unpredicted significant reductions in first trimester bleeding, premature labor, and neonatal respiratory distress were also associated with higher blood lead levels. This study was a retrospective analysis; that is, the investigators themselves did not examine the infants but instead relied on the routine observations of hospital staff pediatric residents, as recorded in chart notes. While ensuring that the data were collected in blind fashion, this method suffers from a lack of precision and uniformity that could have affected the results in various ways. Diagnosing malformations, particularly minor malformations, involves judgment by a clinician as to the degree of departure from normality. The fact that neither major malformations (which would be more obvious) nor any specific minor malformation showed a significant relationship to blood lead level in the analyses of Needleman et al. suggests that diagnostic criteria were not consistently employed. This lack of precision could be the basis for the nonspecificity of their reported effect (i.e., minor malformations taken as a whole but not individually). Clearly, it would be preferable to have specialists in teratology make the diagnoses on the basis of predetermined criteria for minor as well as major malformations. Prior determination of diagnostic criteria and assignment as to their severity would also eliminate the possibility of grouping certain outcomes to achieve statistical significance. On the other hand, diagnostic imprecision would not appear, in itself, to bias the investigation so as to promote detection of a spurious association where none existed.

The multiplicity and apparently exploratory nature of the statistical analyses performed by Needleman et al., coupled with the prima facie implausibility of a protective effect of lead (for first trimester bleeding, premature labor, and neonatal respiratory distress), suggest the possibility that their findings were simply due to chance, i.e., an artifact of conducting multiple statistical tests. However, lead may have highly specific and independent effects within a given organ system (Silbergeld, 1983), so qualitatively different outcomes are not wholly unlikely. In addition, as discussed further below, seemingly paradoxical effects of prenatal lead exposure could be due to misleading indicators of exposure. For example, if in some cases the fetus served as a sink for the mother's body burden, then the maternal blood lead level could be lower than that registered in the cord. Thus, the mother might be "protected" at the expense of the fetus, or vice versa, depending upon the dynamics of the mother-fetus transfer of lead at any particular stage of gestation.

McMichael et al. (1986) followed 749 pregnancies prospectively to completion but also apparently used hospital records to obtain data on congenital malformations. Apart from noting that 40 (5.4 percent) of the infants had anomalies at birth (29 of which were classified as minor), they simply stated, "After controlling for the putative risk factors of maternal age, gravidity, social status, smoking and alcohol usage, no association with blood lead level at 14-20 weeks or later was apparent." Unfortunately, not enough information is provided in their report on their methods or analyses to judge the validity of their conclusion on this point.

The investigation by Ernhart et al. (1985a, 1986) was part of a prospective study using cord and maternal blood samples taken at the time of delivery and employing a detailed protocol for the detection of birth anomalies. Their success in detecting an effect of maternal alcohol consumption (Ernhart et al., 1985b) suggests that their methodology was basically adequate to detect a teratological effect. However, the maternal and cord blood lead levels observed by Ernhart et al. (1986) averaged only 6.5 and 5.8 µg/dl, respectively, with maximum values of 11.8 and 14.7 µg/dl. This restricted range of variation in blood lead levels coupled with a comparatively small number of subjects (n = 185) and the relatively infrequent occurrence of congenital anomalies (often less than 1-2 percent of births) would have made it difficult to detect an effect of lead in any case.

The evidence available from the above three studies allows no definitive conclusion at this time regarding the existence of an association between commonly encountered levels of prenatal lead exposure in humans and the occurrence of congenital anomalies. Further prospective studies with large subject populations and clearly adequate statistical power are needed to resolve this question. For example, if the natural occurrence of a malformation is 2 percent, 5402 subjects per group would be required to find a relative risk of 1.5 with an alpha of 0.05 and a beta of 0.10 (Schlesselman and Stolley, 1982).

More evidence is available that bears on the issue of prenatal lead exposure and the developmental outcomes measured as birth weight and gestational age. All of the studies summarized in Table A-10 included gestational age and birth weight as variables in their analyses, but the only significant findings for birth weight came from Dietrich et al. (1986). No evidence of an association was reported by Ernhart et al. (1985a, 1986), Needleman et al. (1984), and Moore et al. (1982). Although Bellinger et al. (1984) found no evidence of an effect on birth weight *per se*, they did report an exposure-related trend in the percentage of small-for-gestational-age infants (1.2, 2.4, and 8.1 percent for the low, mid, and high blood lead categories).

The findings of McMichael et al. (1986) are not entirely clear with regard to birth weight. The proportion of pregnancies resulting in low-birthweight singleton infants for Port Pirie women (whose blood lead levels averaged 10.4 µg/dl) was more than twice that for

Table A-10. Summary of recent studies on the association of prenatal lead exposure with gestational age and birth weight.

Reference	n	Pb-Exposure Index	Avg. PbB (µg/dl)	Gestational Age	Birth Wt.
Ernhart et al. (1985a, 1986)	185	delivery	6.5	?	0
	162	cord	5.8	?	0
Bellinger et al. (1984)	216	cord	6.5	+	-[1]
Needleman et al. (1984)	4354	cord	6.5	0	0
Dietrich et al. (1986)	185	prenatal	8.3	-*	-*
McMichael et al. (1986)	749	delivery	11.0	-*	+[2]
		cord	10.0	-*	+[2]
Moore et al. (1982)	236	delivery	14.0	-*	0
		cord	12.0	-*	0

Symbols: 0, no evident relationship; +, positive relationship; -, negative relationship; *, statistically significant at $p < 0.05$; ?, not reported.

[1] Birth weight showed no relationship, but the trend in percentage of small-for-gestational-age infants was nearly statistically significant at $p < 0.05$.

[2] See text for possible explanation of reduced blood lead levels in mothers whose infants were low in birth weight.

non Port Pirie women (average blood lead level 5.5 µg/dl). Yet in both groups the mean blood lead levels (maternal as well as cord) for low-birth weight pregnancies were lower than those for birth weights greater than 2500 g. Multiple regression analysis showed no significant association between low birth weight and maternal blood lead. Note that, unlike others who used birth weight as a continuous variable, McMichael et al. categorically defined low birth weight as less than 2500 g at 37 weeks or greater gestational age. This dichotomous classification might have made detection of subtle effects on birth weight more difficult. However, using "small-for-dates" (i.e., weight less than the tenth percentile for the appropriate gestational age) in multiple logistic regression analysis revealed no evidence of intrauterine growth retardation.

It is interesting that McMichael et al. found low birth weight as well as stillbirths associated with lower maternal blood lead level (stillbirths significantly so, birth weight not). These seemingly anomalous findings could be explained by a greater than normal transfer of lead from the mother to the fetus and/or placenta in such cases. As noted in Section 10.2.4 of the revised Criteria Document (U.S. EPA, 1986) and further confirmed by some of the studies reviewed here, maternal and cord blood lead levels are in general highly correlated, with maternal levels at birth typically being somewhat greater than cord levels. However, average blood lead levels at birth may not accurately reflect individual circumstances or past exposure levels. For example, Ong et al. (1985) analyzed maternal and cord blood lead concentrations for 114 women at delivery and found that, although the two were significantly correlated ($r = 0.63$), in roughly one-fourth of the cases the cord blood lead level was higher than the mother's. The dissociation of maternal and fetal blood lead noted by Ernhart et al. (1985a, 1986) in their statistical analyses might also reflect increased transfer and/or absorption of lead from the mother to fetus in certain individuals.

In addition, exposure levels during the course of pregnancy may not be accurately indexed by blood lead levels at parturition. Various studies indicate that average maternal blood lead levels during pregnancy may tend to decline (Alexander and Delves, 1981; Bonithon-Kopp et al., 1986), increase (Gershanik et al., 1974; Manton, 1985), or show no consistent trend (Barltrop, 1969; Lubin et al., 1978). These divergent results may simply reflect the likelihood that the maternal blood lead pool is subject both to increase as bone stores of lead are mobilized during pregnancy (Buchet et al., 1978; Manton, 1985; Silbergeld and Schwartz, 1986) and to decrease as lead is transferred to the placenta and fetus.

Apparently, then, under some conditions the fetus may be exposed to higher levels of lead than indicated by the mother's blood lead concentration. This conclusion does not establish that birth weight is reduced by intrauterine exposure to lead. It does suggest, however, that attempts to detect effects of prenatal lead exposure--including not only birth weight, but morphological anomalies, pregnancy outcomes, and postnatal development--may be complicated if, for some reason, a disequilibrium exists between maternal and fetal body burdens at the time of blood lead measurement. Further research is needed on the dynamic relationship between mother and fetus as lead is mobilized and transferred from one to the other during gestation.

For gestational age, Dietrich et al. (1986), Moore et al. (1982), and McMichael et al. (1986) reported significant negative relationships with prenatal lead exposure; in contrast, Needleman et al. (1984) reported no association, and Bellinger et al. (1984) reported a positive (nonsignificant) relationship between prenatal lead exposure and gestational age. Note, however, that infants of less than 34 weeks gestational age were excluded from the study by Bellinger and his colleagues. This selection criterion would interfere with detection of a reduction in gestational age. Thus, the evidence as a whole from these studies indicates that gestational age appears to be reduced as prenatal lead exposure increases, even at blood lead levels below 15 µg/dl. Based on the parameter estimates of Dietrich et al. (1986), the reduction in gestational age amounts to 0.6 week per natural log unit of blood lead increase. In terms of risk estimates, according to McMichael et al. (1986) the risk of pre-term delivery increases signficantly by at least 4-fold as either the cord blood lead or mother's blood lead concentration at delivery increases from ≦8 to >14 µg/dl.

Further evidence of a deleterious effect of prenatal lead exposure on infant development comes from studies using the Mental Development Index of the Bayley Scales of Infant Development (Table A-11). Bellinger and his colleagues have reported persistent deficits of 4-7 points in MDI scores at ages 6 to 24 months, and have found that these deficits consistently relate to the children's blood lead levels measured at birth in the umbilical cord (Bellinger et al., 1984, 1985, 1986a,b). Dietrich et al. (1986) have also reported deficits on 6-month MDI scores that relate to prenatal maternal blood lead levels. In both of these studies the results were statistically significant after proper allowance for various factors such as SES, HOME scores, tobacco and alcohol usage, etc. Both studies also provide estimates of the magnitude of the effects on MDI scores. Parameter estimates from Bellinger et al. range from -2 to -3.6 points for each increment in cord blood lead classification (see Table A-5). Consistent with these figures is the estimate of -2.25 points per natural log unit maternal blood lead as derived from the structural equation analyses of Dietrich et al. (see Figure A-2).

Vimpani et al. (1985) found evidence more clearly relating MDI deficits to postnatal lead exposure than to prenatal exposure. They ascribed an average 4-point drop in 24-month MDI scores to a mean increase of 10 µg/dl in blood lead levels at 6 months after birth. Note, however, that they also found a negative relationship between MDI scores and average prenatal exposure, although not a statistically significant relationship. Since postnatal blood lead levels increased by about 50 percent from 6 months to 15 months in the Port Pirie study, later increases in exposure may have overwhelmed the more subtle effects of lower prenatal exposure levels. It should be remembered that the same cohort of subjects showed significantly reduced gestational age and possibly other effects as a result of these prenatal exposure levels (McMichael et al., 1986). Also, earlier testing on the Bayley Scales (e.g., at 6 months of age) might have revealed a stronger effect of prenatal exposure than could be detected at 24 months after birth.

The prospective study of Ernhart et al. (1985a, 1986) has thus far provided evidence relating neonatal performance on a Neurological Soft Signs scale (jitteriness, hypersensitivity, etc.) to prenatal lead exposure as reflected in cord blood lead levels. A brief follow-up report by Wolf et al. (1985) indicates that lowered Bayley MDI scores at one year of age appear to be a statistically significant sequela of the cord blood lead effect on Neurological Soft Signs shortly after birth. Finally, Winneke et al. (1985) noted a highly significant relationship between perinatal blood lead levels and one measure of psychomotor performance at 6-7 years after birth.

Table A-11. Summary of recent studies on the relationship between prenatal lead exposure and Bayley Mental Development Index scores.

Reference	n	Pb-Exposure Index	Avg. PbB (μg/dl)	Bayley MDI Scores 6-mo	12-mo	18-mo	24-mo
Bellinger et al. (1984, 1985, 1986a,b)	216	cord	6.5	-*	-*	-	-*
		6-mo PN	6.2	0	0	0	0
		12-mo PN	7.7		0	0	0
		18-mo PN	?			0	0
		24-mo PN	?				0
Dietrich et al. (1986)	185	prenatal	8.3	-*[1]			
		10-day PN	4.9	-			
		3-mo PN	6.3	-*[2]			
		6-mo PN	8.1	+*[3]			
Vimpani et al. (1985)	592	prenatal	?				-
		delivery	11[4]				0
		cord	10[4]				0
		6-mo PN	~14[5]				-*
		15-mo PN	~21[5]				-
		24-mo PN	~21[5]				-
		integr. PN	?				-*

Symbols: 0, no evident relationship; +, positive relationship; -, negative relationship; *, statistically significant at $p < 0.05$; ?, not reported; PN, postnatal.

[1] Effect of prenatal (i.e., maternal) blood lead on MDI mediated through effects on gestational age and/or birth weight.

[2] Effect of blood lead at 3 months significant only for White children (15 percent of study population).

[3] Authors interpret positive relationship as due to greater lead exposure in developmentally advanced children.

[4] Blood lead levels for Port Pirie mothers only, as reported by McMichael et al. (1986).

[5] Geometric means estimated from graph.

The exposure levels at which the above neurobehavioral deficits are observed can be inferred from some of the reported analyses. Based on the blood lead classifications used by Bellinger et al. (1984) and the 95 percent confidence intervals for the effects they reported (see Table A-5), significant declines in Bayley MDI scores occurred at cord blood lead levels of 10 μg/dl and above. Dietrich et al. (1986) did not group the prenatal blood lead concentration in their study, and thus it is not possible to state a precise exposure level at which their effects occurred. However, with a mean of 8.3 and standard deviation of 3.8, it appears that over 95 percent of their study population had blood lead levels below 16 μg/dl. Vimpani et al. (1985) noted that subjects whose blood lead concentrations consistently fell in the top quartile at 6, 15, and 24 months had significantly lower MDI scores compared to the remainder of the cohort. Although the authors did not describe the distribution of blood lead levels in their study, they did note that about 20 percent of the subjects had blood lead levels in excess of 30 µg/dl at age 2 years, which was the point of peak exposure. Thus, their levels appear to be somewhat higher than those of the other studies reviewed here. However, the prenatal levels for this cohort were considerably lower, averaging around 11 µg/dl in Port Pirie mothers and about 8 µg/dl outside Port Pirie (McMichael et al., 1986).

The neurobehavioral effects noted by Ernhart et al. (1985a, 1986) and Wolf et al. (1985), although "small" by the authors' characterization, were significantly related to cord blood lead levels that averaged only 5.8 µg/dl and ranged upward to only 14.7 µg/dl. Winneke et al.(1985) reported that errors in reaction test performance were associated with maternal blood lead levels averaging 9.3 µg/dl and cord blood lead levels averaging 8.2 µg/dl. A scatter plot of the mother-cord blood lead concentrations indicates that, except for a couple of outliers, nearly all of the values were clearly below 20 µg/dl and generally did not appear to exceed about 15 µg/dl. All of these studies taken together suggest that neurobehavioral deficits, including declines in Bayley Mental Development Index scores and other assessments of neurobehavioral function, are associated with prenatal blood lead exposure levels on the order of 10 to 15 µg/dl and possibly even lower, as indexed by maternal or cord blood lead concentrations.

The evidence reviewed in this section supports the conclusion that fetal exposure to lead at relatively low and prevalent concentrations can have undesirable effects on infant mental development, length of gestation, and possibly other aspects of fetal development. Further research is needed to assess the complex dynamic relationship between maternal and fetal body lead burdens, particularly with regard to possible individual differences in transfer and/or uptake from mother to fetus. Further research is also needed to assess the possible contribution of paternal lead exposure to these effects (cf. Uzych, 1985; Trasler et al., 1985; Brown, 1985). At present, however, perinatal blood lead levels at least as low as 10 to 15 µg/dl clearly warrant concern for deleterious effects on early postnatal as well as prenatal development. The persistence of certain types of effects remains to be more fully investigated as the present long-term prospective studies proceed. For example, it remains to be evaluated as to whether delays in cognitive development indicated by decrements in MDI scores are reflected in later childhood by lowered IQ scores or poorer academic performance. The evidence from other studies reviewed in the 1986 Criteria Document (U.S. EPA, 1986) is indicative of decrements in IQ measured in schoolage children, even at PbB levels below 30 µg/dl. Note that additional evidence for IQ decrements being associated with blood lead levels below 30 µg/dl (Hazakis et al, 1986) and, possibly, as low as 10-15 µg/dl (Fulton et al, 1986) in schoolage children was presented at a recent Edinburgh symposium.

3.2 Effects of Lead on Postnatal Growth

3.2.1 Epidemiologic Observations

Among the earliest indications of lead effects on stature in children are observations reported by Nye (1929) regarding "runting," along with squint and foot drop, as physical signs characteristic of overtly lead-poisoned Australian children seen in the 1920's. Remarkably, since then very few systematic evaluations of possible stunting of physical growth have been included among the health endpoints examined in the numerous epidemiologic studies of lead effects on early human development.

In one such study, Mooty et al. (1975) obtained physical measurements (weight, height) for children (2-4 years old) chosen according to low and high blood lead levels ($\bar{x}$ ± S.D.= 20.4 ± 4.3 and 56.9 ± 8.3 µg/dl, respectively). The 21 high-lead children, with blood lead levels in the range 50-80 µg/dl, were both shorter ($\bar{x}$ = 32.1 percentile on Stuart's Boston Growth Charts) and weighed less ($\bar{x}$ = 43.8 percentile) than the 26 low-lead children with blood leads of 10-25 µg/dl (height = 41.1 percentile, weight = 48.7 percentile). The average age for the control group, which was composed of 12 Puerto Rican, 8 Black, and 5 Caucasian children, was 34 months; the high-lead group had a mean age of 33 months and was composed of 4 Puerto Rican, 17 Black, and no Caucasian children. Because of the slightly younger age and lack of Caucasian children in the high-lead group (as well as other differences, e.g., dietary intakes), it is not possible to clearly determine the relative contribution of lead to the observed smaller stature of the high-lead subjects versus other factors.

In a later study, Johnson and Tenuta (1979) studied the growth and diets of 43 low-income Milwaukee children (aged 1-6 years) in relation to their blood lead levels. Children with low (12-29 µg/dl; N = 15), moderate (30-49 µg/dl; N = 16), and high (50-67 µg/dl; N = 12) blood lead levels had average daily calcium intakes of 615, 593, and 463 mg, respectively. Also, there was a relative decrease ($p < 0.075$) in individual height percentile with increasing blood lead level (high-lead children had means of 25.7 percentile for height and 42.2 percentile for weight; no specific data were reported for other lead groups) and higher incidence of pica (eating of plaster and paint) on the part of the children with blood lead levels ranging from 30 to 67 µg/dl. Unfortunately, the specific racial composition and mean ages of the different blood lead groups were not reported, making it impossible to determine the relative contribution of such factors (or the differences in calcium intake or other dietary factors) to the observed smaller stature among the high-lead children.

In another study, Routh et al. (1979) examined a sample of nonurban children (N = 100; mainly from lower socioeconomic status families in North Carolina) with developmental and learning disabilities for previously undiagnosed lead intoxication. One child with "moderately" elevated blood lead (according to the then-existing CDC classification, 50-79 µg/dl) and nine with "minimal" elevations (30-49 µg/dl) were identified. Of these 10 children, seven were microencephalic (defined as head circumferences at or below the third percentile for the child's age on standard growth charts). This was a markedly greater proportion of microencephaly than that seen among the remaining children with blood lead levels below 29 μg/dl (17 of 62; 25 percent). Most of the microencephaly syndrome children were Black. Five of the elevated blood-lead children also showed more general growth retardation, in that their height, weight, or both were at or below the third percentile for age and sex. These results, as are those from the previously discussed studies, are suggestive of possible stunting of growth due to lead exposure early in development resulting in blood lead levels generally above 30 μg/dl. However, again it is not possible to clearly separate the relative contribution of lead from other factors (racial, dietary, etc.) that may have affected growth of the children studied by Routh et al. (1979).

Much stronger evidence for lead exposure producing retardation of growth and decreased stature has more recently emerged in the 1980's from both animal toxicology studies (discussed below) and evaluation of larger scale epidemiologic data sets. In regard to the latter, Schwartz et al. (1986) have reported results of analyses of data from the NHANES II study described earlier in relation to evaluation of blood lead/blood pressure relationships. More specifically, Schwartz et al. (1986) analyzed results for anthropometric measurements, as well as numerous other factors (age, race, sex, dietary, etc.) likely to affect rates of growth and development, among the NHANES II children.

Linear regressions of adjusted data from 2695 children (aged 7 yrs or younger) indicated that 9 percent of the variance in height, 72 percent of the variance in weight, and 58 percent of the variance in chest circumference were explained by the following five variables: age, race, sex, blood lead, total calories or protein, and hematocrit or transferrin saturation. The step-wise multiple regression analyses further indicated that blood lead levels were a statistically significant predictor of childrens' height ($p < 0.0001$), weight ($p < 0.001$) and chest circumference ($p < 0.026$), after controlling for age in months, race, sex and nutritional covariates. The strongest relationship was found between blood lead and height, with threshold regressions indicating no evident threshold for the relationship down to the lowest observed blood lead level of 4 μg/dl. At their average age (59 months), the mean blood lead level of the children appears to be associated with a reduction of about 1.5 percent below the height expected if their blood lead level had been zero. Similarly, the relative impacts on weight and chest circumference were of the same magnitude.

Overall, the above findings of Schwartz et al. (1986) appear to be highly credible, being based on well-conducted statistical analyses of a large-scale national survey data set (which was subjected to rigorous quality assurance procedures) and having taken into account numerous potentially confounding variables. Other recent results newly emerging from independent, well-conducted prospective studies of prenatal and early postnatal lead exposure effects on human development, also appear to substantiate the likelihood of lead retarding early growth, as reviewed above. For example, Dietrich et al. (1986) report that prenatal maternal blood lead levels and early postnatal (10-day) blood lead levels were negatively correlated with birth weight ($p < 0.001$) and gestational age ($p < 0.05$) for 185 infants from low socio-economic inner-city Cincinnati families. The plausibility of reported epidemiologic findings of associations between early lead exposure and retardation of growth reflecting a causal relationship is supported by animal toxicology results concisely discussed below.

3.2.2 Animal Toxicology Studies

The impairment of physical growth or stature as an effect of lead exposure during prenatal or early postnatal life has been well established by animal studies (see below). However, although preceeding sections of the Addendum cite several recent epidemiological studies which strongly support the notion that lead exposure during early development can lead to retardation of growth in humans as well, additional carefully designed animal toxicology studies are needed to better substantiate and further extend the epidemiological findings.

A computer search for the relevant animal experimental studies published during the last decade yielded 43 papers which described significant retardation of growth (measured by gain in weight or length) after low-level exposure during intrauterine life, during early postnatal life, or both. An additional 22 papers specifically stated that growth of the lead-exposed animals was not affected. However, a close examination of this latter group of studies revealed that in the great majority of the cases the treatment started too late (e.g., after weaning) or the doses were too low (e.g., less than 10 ppm in drinking water). On balance, then, it seems very clear that low-level chronic lead exposure during pre- and early postnatal development does indeed result in retarded growth even in the absence of overt signs of lead poisoning.

One study on rats, by Grant et al. (1980), provides detailed experimental data relating external lead exposure doses to consequent blood lead levels and growth rate measured in terms of both weight and length. Continuous prenatal and postnatal exposures to lead were accomplished via lead adulteration of the drinking water: (1) of dams prior to conception, throughout pregnancy, and nursing; and (2) of the drinking water consumed post-weaning by their offspring through 180 days (6 months). Females from lead exposure groups with average blood lead levels in the range of 18-48 μg/dl were significantly shorter in crown-to-rump length from postnatal days 7 to 180; lead-exposed males exhibited only a transient retardation of growth and were not significantly different in length from control animals by the end of the 180 day observation period. Decreased body weight (with no decrease in food consumption per unit of body weight) was found in animals with blood lead levels of 40-60 µg/dl, whereas deficits in rate of neurobehavioral development and indications of specific organic or functional alterations (Fowler et al., 1980) were observed at blood lead levels in the range of 20-40 µg/dl.

3.3 Possible Mechanisms of the Effects of Lead On Growth and Development

Considering the numerous reports of growth impairment in lead-exposed experimental animals, as well as emerging evidence concerning similar effects in human subjects, it is surprising to find that out of the more than 60 studies alluded to above, none was specifically designed to investigate the mechanism of lead-induced growth retardation, and only a very few even commented upon possible, speculative mechanisms. Thus, it can clearly be concluded that experimental studies specifically addressing this question are needed.

What are the mechanisms to be considered? At the low dose levels of interest (those relevant to human populations), general malaise resulting from severe poisoning or one or more of its manifestations, e.g., marked damage to blood, brain, kidney, or the cardiovascular system, are not likely to be important. On the other hand, consideration of established factors that affect the regulation of normal growth may enable one to identify measurable parameters that are likely to be affected by lead.

Growth is a complex phenomenon that is accompanied by an orderly sequence of maturational changes which involve accretion of protein and increases in length and size, not just weight. While growth hormone (GH) is the most abundant hormone of the pituitary gland, and its primacy in controlling postnatal somatic growth is unquestioned, growth is also affected by thyroid hormones, androgens, estrogens, glucocorticoids, and insulin. Extrinsic and genetic factors also play a part in regulating growth.

3.3.1 Genetic and Extrinsic Factors

Food supply is the most important extrinsic factor affecting growth. Food must be adequate in proteins, essential vitamins, minerals, and calories. Several studies have demonstrated that nutritional deficits aggravate the effects of lead poisoning (e.g., Bell & Spickett, 1983; Hsu, 1981; Leeming & Donaldson, 1984; Ashraf & Fosmire, 1985; Woolley and Woolley-Efigenio, 1983; Harry et al., 1985).

3.3.2 Endocrine Factors

The major hormones that are involved in postnatal growth are GH, thyroid hormones, and androgens. These should be measured in the blood of lead-exposed animals during the critical stages of life and correlated with growth and developmental parameters. Practically none of this information is available at this time. Of the many animal studies reviewed (plus many other human studies), none included GH measurements in the lead-exposed growth-impaired subjects. However, known facts regarding neuroendocrine control of GH secretion and potential effects of lead on such neuroendocrine regulatory mechanisms provide plausible hypotheses regarding ways by which lead-induced growth retardation could be mediated.

The secretion of GH from the pituitary is controlled by the hypothalamus. Two neuropeptides, a stimulating one (GRF) and an inhibiting one (SRIF), have been isolated and characterized. In addition, dopamine (DA) appears to be important in GH regulation, although its effects (which may be exerted at several different levels) are not entirely clear. These substances can now be assayed in blood and in small pieces of tissue, and the neurons which produce them can be identified by immunohistochemical methods. It is not yet known in detail how GH secretion is regulated. GH itself can inhibit its own secretion via a so-called short-loop feedback mechanism. The anatomical substrate for such a mechanism has been demonstrated when it was shown that blood in some of the hypothalamo-hypophysial portal vessels does actually flow upward, from the pituitary to the hypothalamus. This blood supply reaches the area of the arcuate nucleus where the GRF-containing neurons are located. SRIF may influence GH release not only directly at the level of the pituitary but also via interactions within the median eminence, and through innervation of the GRF-producing cells in the arcuate nucleus. The reverse interaction may also occur, i.e., GRF, via axon collaterals ending in the vicinity of SRIF-producing neurons in the anterior periventricular area of the hypothalamus, may influence the production and release of SRIF. Finally, somatomedin (SM) may play an important role in the GH-regulating feedback mechanisms (cf. Underwood and van Ryk, 1985, and discussion below). Direct injection of SM into the cerebral ventricles has been shown to inhibit GH secretion. This can occur by at least two mechanisms: stimulation of SRIF production in the hypothalamus, and inhibition of the synthesis of GH in the pituitary in response to GRF.

Endogenous opiates (enkephalins and endorphins) are also known to stimulate the release of GH, probably through activation of hypothalamic mechanisms (e.g., Casanueva et al., 1980). In the only study which looked at the effects of perinatal lead exposure on enkephalin levels in one brain region, namely the striatum (Winder et al., 1984), up to a 50 percent decrease was found; however, enkephalin levels in the hypothalamus of lead-intoxicated animals were not investigated.

Although the effects of lead on the nervous system have been studied extensively, no study has so far attempted to determine its influence on hypothalamic releasing or inhibiting factors, including GRF and SRIF. One recent study addressed the question of how chronic lead treatment influenced the dopaminergic control of prolactin, a pituitary hormone whose regulation is similar to that of GH (Govoni et al., 1984). Although DA content in the hypothalamus was unchanged, the content of one of its metabolites, dihydroxyphenyl acetic acid, showed a highly significant decrease. The amount of DA receptors in the pituitary was also decreased. These findings explain, at least partially, previous findings that circulating prolactin levels were elevated in chronically lead-exposed rats (Govoni et al., 1978). The importance of DA in the control of normal growth is emphasized by a recent study by Huseman et al. (1986), in which they establish endogenous dopaminergic dysfunction as a possible cause of human growth hormone deficiency and short stature. According to these authors, decreased GH production can result from decreased dopaminergic or noradrenergic tone in the hypothalamus, from decreased GRF production by hypothalamic neurons, and finally from decreased pituitary responsiveness to GRF and/or DA. All these parameters can now be measured and should be carried out in studies of chronically lead-exposed animal models.

As pointed out above, it has become clear that many (but not all) effects of GH are mediated by peripherally produced growth factors called somatomedins (SM). These interact with receptors in target tissues, the most important of which from the point of view of linear growth is cartillage. Only one study (Rohn et al., 1982) is so far available in which SM levels were correlated with lead intoxication in 21 children before and after chelation therapy. Somatomedin levels in these children were found to be increased, and became further elevated after chelation; plasma GH or other pituitary hormones were not determined. The mechanism of the changes found in this study is not clear, but the most likely explanation is that some sort of compensatory overproduction of SM was occurring. Again, experimental studies of the appropriate design would be most useful.

Somatomedin secretion is reduced in diabetes and can be restored by insulin treatment. The overlapping biological activities of insulin and SM might be due to the fact that these two hormones react with each other's receptors. Insulin is clearly the primary stimulator of somatic growth in the fetus, and in postnatal life insulin deficiency (diabetes) is associated with growth failure, while hyperinsulinism is accompanied by overgrowth in several conditions. None of the references found in the literature survey alluded to above addressed the question of whether lead affects insulin secretion in the fetus or during early postnatal life.

With regard to thyroid function, impairment of the iodine-concentrating mechanism by lead has been shown in rats (Sandstead, 1967) and in man (Sandstead et al., 1969). In addition, one of two patients studied had decreased secretion of thyroxine. Since the iodine-uptake deficit was readily corrected by the injection of thyroid stimulating hormone (TSH), it can be assumed that TSH deficiency was at least a factor in these patients. However, neither in this nor in any other studies were direct measurements of thyroid hormone (or TSH) levels have been performed at the ages when the involvement of these hormones in growth is critical.

Androgens in lead-exposed animals have been measured only in one recent study (Sokol et al., 1985) which was designed to evaluate the effects of lead on the hypothalamo-pituitary-testicular axis in post-pubertal (52- to 82-day old) rats. Significantly reduced levels of testosterone were found both in testicular tissue and in blood. Also, the weight of the ventral prostate (a sensitive indicator of androgen activity) was reduced.

The androgens responsible for the peripubertal growth spurt orginate from the adrenal cortex, which (perhaps through the hypothalamo-pituitary axis) is also affected by lead (Sandstead et al., 1970b). However, other steroids besides androgens may also be important here. For example, the inhibition of growth in immature animals is one of the cardinal effects of glucocorticoids. Again, specific studies assessing the possible involvement of the adrenal gland in the effect of lead on growth are completely lacking.

3.3.3 Additional Factors Affecting Growth

There are additional growth factors other than those discussed above. These include some broad-spectrum, hormone-like growth factors such as epidermal growth factor, platelet-derived growth factor, and fibroblast growth factor, as well as more restricted, tissue-specific growth factors such as nerve growth factor, erythropoietin, colony-stimulating factors, and lymphocyte growth factors (interleukins). The great importance of these growth factors -- besides their specific roles in particular tissues and growth processes -- lies in the fact that several of them (or their receptors) have been found to be related to oncogenes and their products, i.e., substances that are responsible for malignant transformation of cells. These or similar substances are now being recognized with increasing frequency as normal constituents of cells and regulators of normal cell growth. The loss of cellular control over the production or function of these substances may be responsible for malignant growth. These growth factors and related gene products have been recognized only recently and are the subject of intensive current research. Thus, it is not surprising that they have not yet been correlated with lead toxicity. However, given the general effects of lead on body growth, it seems quite likely that one or more of these growth factors or oncogene products may be influenced by lead toxicity.

3.4 Summary and Conclusions Regarding Lead Effects on Growth and Development

The earlier epidemiologic studies discussed above (Mooty et al., 1975; Johnson and Tenuta, 1979; Routh et al., 1979) provided suggestive evidence for lead effects on early growth and stature. However, it is difficult to apportion relative degrees of contribution of lead to observed growth deficits in comparison to other factors due to the manner in which the data from these small scale studies were reported. Much stronger evidence has emerged from the Schwartz et al. (1986) evaluation of the large-scale NHANES II nationwide data set, and some additonal data are beginning to emerge from prospective studies, such as that of Dietrich et al. (1986).

The plausibility that the observed epidemiological associations between lead exposure and retarded growth reflect causal relationships is supported by certain limited parallel experimental toxicology observations in numerous animal studies, including especially findings reported in the rat by Grant et al. (1980), albeit at blood lead levels distinctly higher than the lower values in the range of blood lead levels of children included in the Schwartz et al. (1986) analysis. Furthermore, the possibility of lead effects on neuroendocrine mechanisms mediating lead-induced retardation of growth is also supported by certain studies, e.g., those of Petrusz et al. (1979) and others, showing effects of lead in neuroendocrine functions in animals and man. In view of the lack of thorough evaluation of lead effects on GH and other plausible mechanisms affecting growth, much remains to be done, however, with regard to more fully characterizing quantitative relationships between lead exposure and growth retardation in children, as well as determining the specific physiological mechanisms underlying such effects.

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